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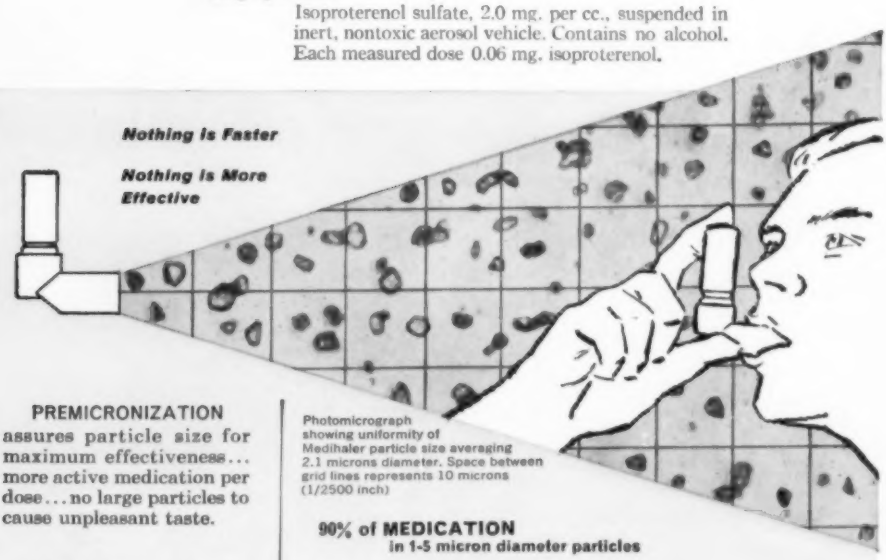

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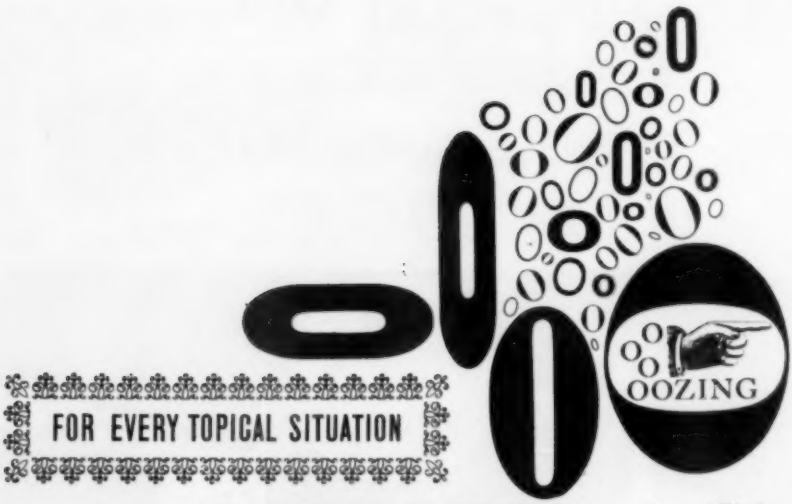

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2. Frank, L.: A.M.A. Arch. Dermat. 75:876, 1957.
3. Welsh, A. L.: Internat. Rec. Med. 169:775, 1956.
4. Robinson, H. M., Jr., et al.: Antibiotic Med. 3:461, 1956.
5. Janssens, J.: Le Scalpel 111:69, 1958.
6. Berreston, E. S.: Clinical Review 1:13, 1958.

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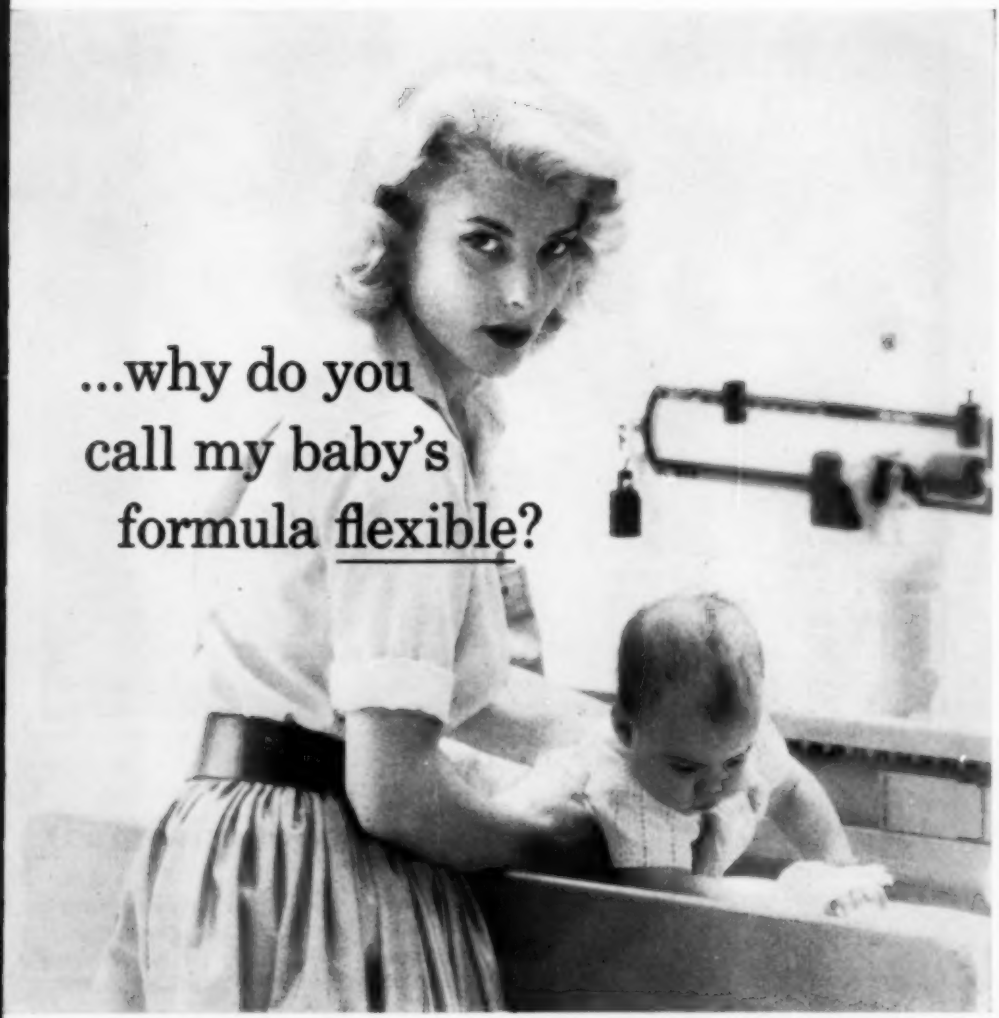

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Serious Coxsackie Infection in Infants and Children

Myocarditis, Meningoencephalitis, and Hepatitis

D. M. HOSIER, M.D., and W. A. NEWTON Jr., M.D., Columbus, Ohio

Coxsackie viruses are considered to be among the most prevalent of recognized viruses. They are known to cause herpangina, epidemic pleurodynia, and aseptic meningitis, but until recently they have not been thought to cause death. To date, five reports have described fatal myocarditis in newborn infants caused by Type B-3 or B-4 Coxsackie virus.[1-5] Four of these reports originated abroad, in South Africa, and described epidemics of fatal myocarditis occurring in newborn infants during epidemics of pleurodynia or aseptic meningitis or both in the population at large.

We are reporting the isolation, during a nonepidemic period, of a Coxsackie Group B Type 4 virus at autopsy from the myocardium of a 7-week-old infant who died in heart failure and from the myocardium, liver, lung, and kidney of a 14-day-old infant who died of sepsis of unknown cause.

A 5-year-old boy recovered completely from myocarditis during which Group B Type 2 Coxsackie virus was isolated from the stool, with a subsequent rise of the homologous serum neutralizing antibodies.

Report of Cases

CASE 1.—A 7-week-old boy was admitted to the hospital on Aug. 8, 1957. He was born prematurely, weighing 5 lb. 2 oz. at birth. There were no maternal illnesses during pregnancy, and he appeared normal at birth. He was considered to be progressing well until 10 days prior to his admission, at which time he developed a cough and a fever (temperature to 103 F). He was thought to have an upper respiratory infection. He received penicillin by injection and by mouth, during the next few days; however, he vomited frequently and became anorexic. He did not appear to improve, and the day prior to his admission he became extremely dyspneic and lethargic.

There was no history of illness in any other member of the family prior to or following the patient's illness.

Physical examination revealed a boy weighing 7 lb. 6 oz., who was dyspneic and unresponsive. The skin was ashen gray; pulse rate, 180 per minute; respiratory rate, 80 per minute, and the temperature was not recordable. Pulses were weak but palpable in all extremities. The ears, nose, and throat were clear. The heart was enlarged, with muffled heart tones and a gallop rhythm. No murmur was detected. The lungs were clear. The liver was palpated 4 cm. below the right costal margin, and the spleen tip was palpable.

A roentgenogram of the chest showed moderate generalized cardiac enlargement. An electrocardiogram showed low voltage in all leads (Fig. 1).

Laboratory data obtained on admission were as follows: RBC, 2,800,000 cells per cubic millimeter; hemoglobin, 8.7 gm. per cubic millimeter; WBC, 19,150 cells per cubic millimeter, with 75% lymphocytes and 24% neutrophils. Blood culture grew a coagulase-negative Staphylococcus. Complement-fixation studies of serum drawn on admission were negative for mumps, lymphocytic choriomeningitis, Eastern equine encephalomyelitis, Western equine encephalomyelitis, St. Louis encephalitis, and Coxsackie B-3 and B-4.

Hospital Course

The infant was placed in oxygen and given lanatoside C (Cedilanid) intravenously. There was

Submitted for publication June 27, 1958.

Departments of Pediatrics and Pathology, Ohio State University College of Medicine.

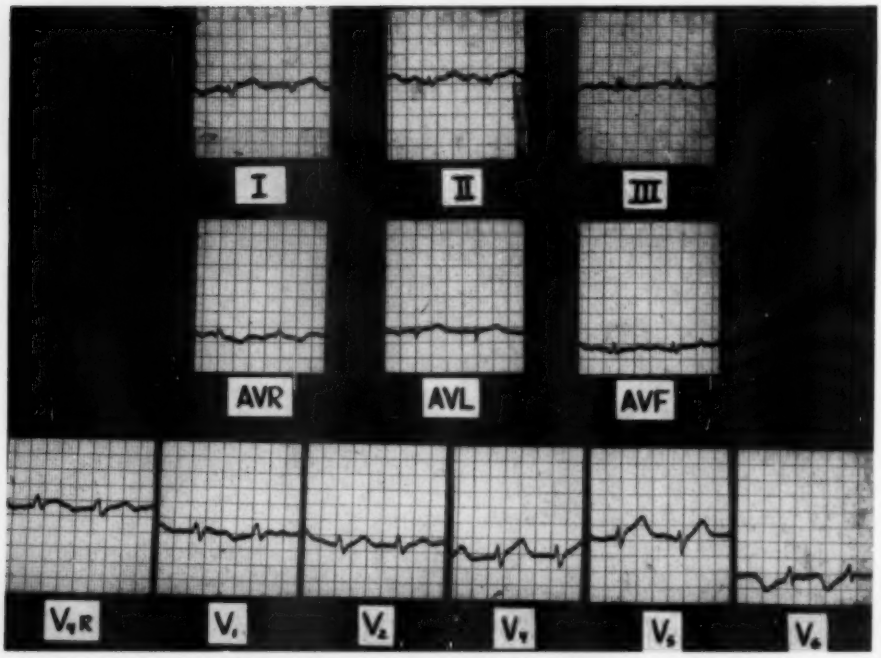


Fig. 1 (Case 1).—Electrocardiogram taken on admission, showing low voltage in all leads. (Paper speed 50 mm. per second.)

no improvement noted, and he died approximately four hours after admission.

Autopsy Report

A complete autopsy was performed six hours after death. The white boy weighed 3460 gm. and measured 54.5 cm. in length. The heart was dilated and flabby in consistency and weighed 45.5 gm. (normal weight 21 gm.). There was no cardiac anatomic malformation. The foramen ovale was anatomically patent, measuring 5 mm. in diameter, but was functionally closed. The endocardium was not thickened. The ductus arteriosus was patent only to a fine hairpin probe.

Both lungs were heavy and less crepitant than normal and showed a moderate amount of frothy fluid on the cut surface when pressure was applied.

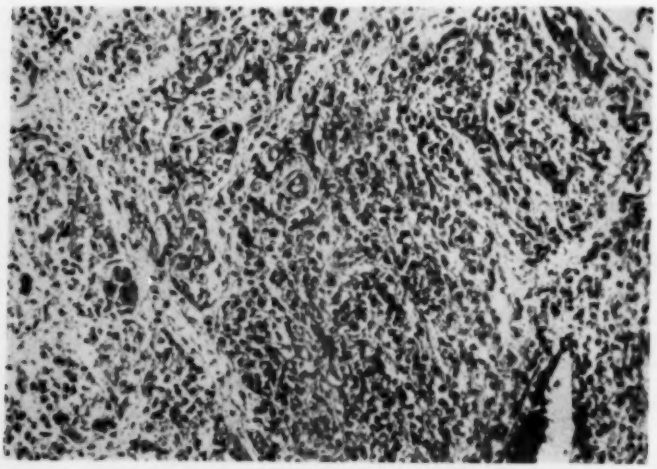


Fig. 2 (Case 1).—Medium-power photomicrograph of myocardium, showing the marked degree of necrosis of the myocardial muscle bundles and the secondary inflammatory cellular reaction.

The liver, brain, and spleen were moderately increased in weight. Blood taken from the left atrium yielded no growth on culture.

No ascites or hydrothorax was present. A portion of the myocardium was stored at —20 C.

Microscopic examination was made of all major organs, fixed in Zenker's acetic fluid, by routine hematoxylin and eosin sections.

The myocardium showed diffuse involvement in sections taken from all chambers. There was marked infiltration with polymorphonuclear neutrophils and lymphocytes and macrophages throughout the interstitial tissue, associated with varying degrees of degenerative change of the myocardial fibers (Fig. 2). The epicardium and endocardium showed minimal change. No viral inclusion bodies or bacteria were seen.

The lung sections showed marked congestion and pulmonary edema.

No evidences of necrosis or inflammation were found outside of the heart, including the brain.

The myocardium saved at —20 C was sent to the Ohio Department of Health Laboratories for virus-isolation studies. A virus was isolated and typed as Coxsackie-type Group B Type 4.

Case Summary

A 7-week-old boy died with clinical evidences of heart failure following a 10-day illness. The autopsy findings consisted of a severe necrotizing inflammation of the myocardium and evidences of cardiac failure elsewhere. Coxsackie virus Group B Type 4 was isolated from the myocardium. A blood culture yielded no growth.

Case 2.—An infant girl was admitted to the hospital on Aug. 31, 1957, at 8 days of age, because she had not taken feedings well since birth. She was born after a full-term gestation. The mother had a kidney infection at term, and the membranes were artificially ruptured a few hours prior to delivery. After delivery the infant was placed in oxygen for 24 hours because of excessive mucus and dyspnea. No further difficulty was encountered after the first day, and she was discharged from the nursery on the fifth day of life. After discharge, however, she began taking feedings poorly and progressively lost weight. Twenty-four hours prior to her admission to this hospital she was noticed to be jaundiced and began vomiting frequently.

On admission she appeared acutely ill. The temperature was 96.8 F rectally; respirations, 45 per minute, and pulse, 120 per minute. She was icteric and very lethargic. The examination of the ears, nose, and throat revealed no abnormality. The fontanel was soft, and the neck, supple. The lung fields were clear to auscultation bilaterally. Examination of the heart revealed no abnormalities. The liver was palpable 2.5 cm. below the right costal margin, and the spleen tip was palpable. Pulses were palpable in all extremities. A diagnosis of sepsis was considered at this time.

A roentgenogram of the chest was not considered abnormal. On the second hospital day a repeat roentgenogram of the chest revealed moderate cardiac enlargement.

Laboratory Data

Hemoglobin, 14.7 gm. per 100 cu. mm.; WBC, 12,200 per cubic millimeter, with 78% lymphocytes, 1% eosinophils, and 21% neutrophils. Urinalysis showed a specific gravity of 1.027, WBC 3 to 4 per high-power field, acetone and albumin negative. Nasopharyngeal and throat cultures revealed no pathogenic organisms. Multiple blood cultures during the hospitalization were sterile. Three days after admission WBC was 22,700 per cubic millimeter, with 54% neutrophils, 1% eosinophils, and 45% lymphocytes. Serum electrolyte concentrations on the third hospital day were as follows: CO_2, 15 mEq. per liter; chloride, 91 mEq. per liter; sodium, 116 mEq. per liter; potassium, 5.9 mEq. per liter. On the fourth hospital day plasma prothrombin was 16.5%; BUN, 18.5 mg. per 100 cc.; CO_2, 17.2 mEq. per liter; chlorides, 102.6 mEq. per liter; sodium, 136 mEq. per liter; potassium, 4.3 mEq. per liter; total protein 4.2 gm. per 100 cc., with albumin 2.7 gm. per 100 cc. and globulin 1.5 gm. per 100 cc. On the fifth hospital day the WBC was 26,400 cells per cubic millimeter, with 72% neutrophils, 1% eosinophils, 2% monocytes, and 25% lymphocytes.

Hospital Course

The infant was given fluids and tetracycline intravenously. Streptomycin was given intramuscularly. The temperature remained subnormal during the entire hospitalization. On the day after admission dark blood-tinged mucus drained from the mouth. On the third hospital day the infant's respirations were noted to be 120 per minute and fine rales were heard in both bases. At this time the infant appeared somewhat edematous. Chloramphenicol (Chloromycetin) was administered, and electrolytic solutions were adjusted to correct electrolyte imbalance. Whole blood and phytonadione (Mephyton) were given in an attempt to correct the low prothrombin level. The respiratory rate continued to be elevated, and the liver gradually enlarged. The infant died on the sixth hospital day.

Autopsy Report

Complete autopsy was performed two hours after death. The baby girl weighed 3310 gm. and measured 51 cm. She showed moderate icterus of the sclerae and mucous membranes.

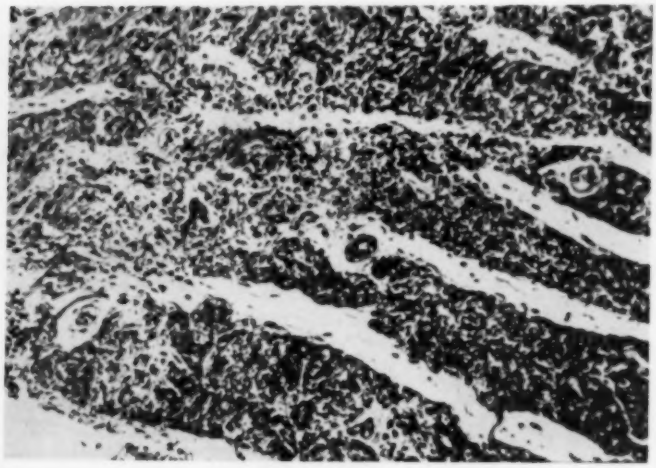


Fig. 3 (Case 2).—Medium-power photomicrograph of the myocardium. Note the focal necrosis of the myocardial muscle bundles and the associated inflammatory cellular reaction.

The heart weighed 33 gm. (normal weight, 19 gm.) and appeared to be slightly dilated. The myocardium was somewhat flabby and was light brown. There was no cardiac anatomic malformation. The foramen ovale was patent, measuring 6 mm. in diameter. The ductus arteriosus was patent, measuring 6 mm. in circumference.

The lungs were not increased in weight, and were crepitant and pink, except for numerous dark red-black spots. No edema fluid could be expressed from their cut surfaces.

The liver weighed 131 gm. (normal weight, 123 gm.). It was red-brown and showed a superimposed fine pin-point stippling of a darker red-brown over all surfaces.

The gross examination of the kidneys, adrenals, brains, and the remainder of the body was not remarkable.

Portions of the myocardium, liver, kidney, and lung were stored at —20 C. Cultures taken from lung, spleen, liver, and ascitic fluid yielded no growth. Blood taken from the left auricle yielded Alcaligenes faecalis (Bacillus alcaligenes). This is considered to be a contaminant.

Microscopic studies of the heart showed foci of degeneration and necrosis of the myocardial fibers throughout the heart (Fig. 3). Inflammatory reaction was minimal in most areas, except of the atrial walls, where a mild to moderate infiltration of macrophages, lymphocytes, and an occasional polymorphonuclear neutrophil was seen in the interstitial tissue. The endocardium and epicardium showed little or no change.

The lung sections showed foci of intra-alveolar hemorrhage and moderate congestion.

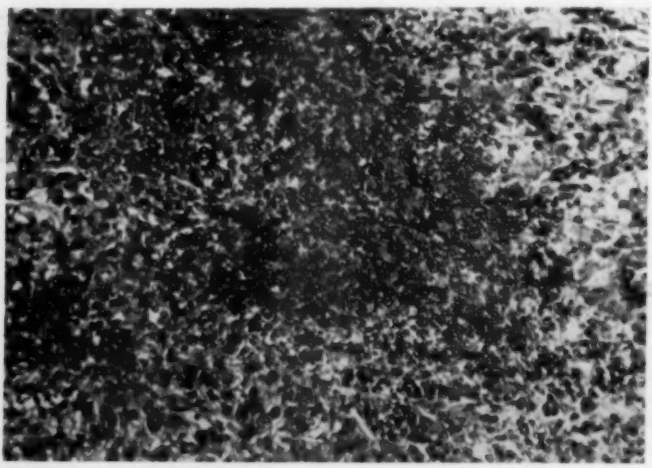


Fig. 4 (Case 2).—Medium-power photomicrograph of liver, showing focal necrosis of the parenchymal cells with associated hemorrhage, without inflammatory cellular reaction.

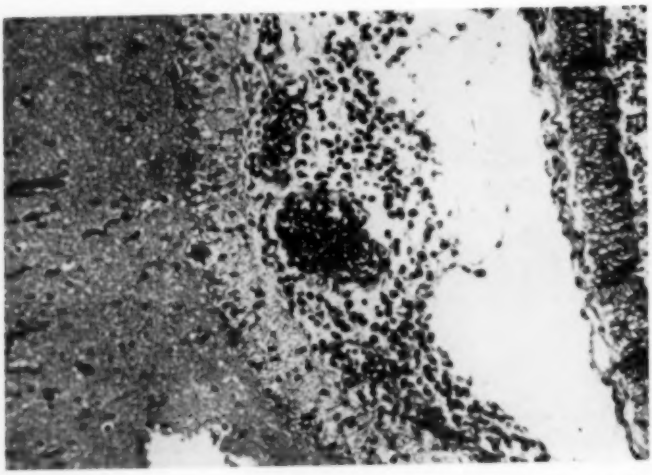


Fig. 5 (Case 2).—Medium-power photomicrograph of cerebral cortex, showing moderate mononuclear cellular infiltration of the meninges.

The liver sections showed extensive foci of hemorrhagic necrosis of the parenchymal cells, involving 40% to 50% of the liver tissue (Fig. 4). There was no significant inflammatory reaction; no viral inclusions and no organisms were present.

The meninges of the brain and spinal cord showed a mild infiltration with mononuclear cells and an occasional polymorphonuclear neutrophil (Fig. 5). A few capillaries and arterioles showed perivascular inflammatory-cell infiltration, again chiefly mononuclear in type. In contrast, the choroid plexus showed moderately severe infiltration with polymorphonuclears (Fig. 6).

With the exception of one small focus in the adrenal, no significant changes were seen elsewhere. One small area of the adrenal cortex showed mild degeneration of the cortical epithelium, chiefly in the zona glomerulosa, with a mild mononuclear-inflammatory-cell infiltrate in the involved area. The sections of the kidney showed no significant changes.

The tissue stored at —20 C was sent to the Ohio Department of Health Laboratories, where abundant growth of Coxsackie virus, type Group B-4 was isolated from all tissues submitted. It is unfortunate that the organs were stored by us in one container. It was felt, however, that each specimen had more virus present in it than could be expected from contamination. Tissue culture ID_{50} of these tissues after seven months' storage at —20 C was as follows: heart $10^{-5.00}$; kidney $10^{-3.5}$; liver negative 10^{-1}, positive undiluted; lung negative.

Case Summary

A child was hospitalized with a diagnosis of sepsis at 8 days of age, showing jaundice

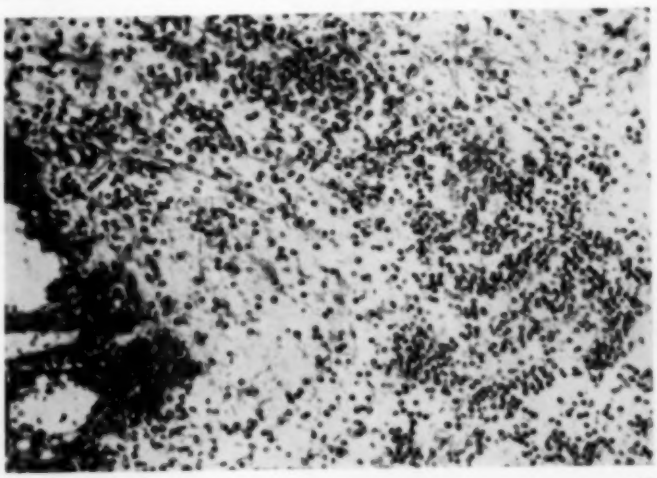


Fig. 6 (Case 2).—Medium-power photomicrograph of choroid plexus, showing marked polymorphonuclear cellular infiltration of this structure.

and lethargy. She developed a progressive cardiac lesion and a bleeding tendency and died after an illness of approximately nine days. Postmortem examination showed extensive focal necrosis of the heart and liver, a mild meningoencephalitis, and focal necrotizing infection of the adrenal. Coxsackie virus, type Group B-4, was isolated from the heart, liver, kidney, and lung.

CASE 3.—A white boy was the fourth child of an Rh-negative mother. Pregnancy had been uneventful until sudden onset of abdominal pain, associated with a drop in maternal hemoglobin. A cesarean section was done promptly, on Sept. 3, 1956, five weeks before the expected date of confinement. Shortly after birth the child developed respiratory difficulty and was transferred to the Children's Hospital. The three previous siblings were not jaundiced or anemic. The father, a pediatrician, had been hospitalized with chest pain and fever 1 month prior to delivery of the child, and the baby's mother developed chest pain and a pleural friction rub 24 hours after delivery. Epidemic pleurodynia was prevalent in the community during the summer months of this year.

On admission the baby showed cyanosis of the lips and nailbeds and respirations were rapid and labored and were accompanied by an audible expiratory wheeze. He weighed 6 lb. 4 oz. The pulse rate was 158 per minute; respiratory rate was 58 per minute, and the temperature was 96.6 F. He was listless; no Moro or deep tendon reflexes could be elicited. Examination of the heart was not remarkable. Breath sounds were not well heard throughout the right lung field. The liver was palpable 2 fingerbreadths below the costal margin.

On admission bilirubin (van den Bergh) was 1.75 mg. % indirect, 0.25 mg. % direct. Hemoglobin concentration was 18.3 gm. per 100 cc.; leukocyte count was 12,300 per cubic millimeter, with a differential count of 72% neutrophils, 27% lymphocytes, and 1% eosinophils. There were 4 nucleated red cells per 100 white cells. The mother's blood type was A, Rh-negative; the baby's blood type, ABcDE (e). The maternal serum showed an anti-D (anti-Rh) titer of 1:4 in saline and 1:16 against trypsin-modified red cells. VDRL test was negative.

Hospital Course

The child was placed in an incubator with added humidity and oxygen, and was given crystalline trypsin (Tryptar) aerosols during the first three days of hospitalization. After 24 hours there was slight improvement in the respiratory difficulty. Retractions of the subcostal margin were still present, but breath sounds had become more audible throughout both lung fields. The baby's temperature was unstable, varying from 96 to 100 F. Admission roentgenogram of the chest had shown minimal granularity. Recheck film, on Sept. 4, 1956, showed incomplete clearing of the granularity. Two days prior to death repeat film showed pneumonia at the base of the right lung.

He was treated with penicillin and dihydrostreptomycin (Combiotic) throughout the hospital stay. Attempts at oral feeding were not successful, and oral gavage by gastric polyethylene tube was begun on the fourth day of life. On the sixth day he suddenly developed severe respiratory distress. He was thought to be in cardiac failure, and lanatoside C was given intravenously. He bled excessively from a needle puncture site and from his nose and was given phytonodione (vitamin K_1), intravenously. He died several hours after the onset of this acute episode. The serum bilirubin rose slowly to a high of 0.25 mg. % direct, 17.0 mg. % total, just prior to death.

Autopsy Report

Complete autopsy was performed one hour after death. The patient weighed 2350 gm. and measured 47 cm. in crown-heel length. There were 4 to 5 cc. of clear viscid yellow ascitic fluid present in the abdomen. The heart was moderately enlarged by weight (23 gm. compared with a normal of 20 gm.) but showed no malformation. The right lung weighed 33.5 gm., and the left lung weighed 28.5 gm. (normal combined weight, 49.5 gm.). Both lungs were pink-cream in color but noncrepitant, except for the anterior third of the right upper and middle lobes. No fluid could be expressed from the cross sectioned surface. The liver and spleen were not enlarged, weighing 106.5 gm. and 9 gm., respectively. The brain weighed 310 gm. (normal weight, 332 gm.). No gross hemorrhage was noted. There was a generalized pale yellow discoloration of the surface and cross section of the brain, but there was no localized yellow staining of the areas usually involved in kernicterus.

Culture of heart blood and ascitic fluid yielded Escherichia coli.

Microscopically, the most marked changes were seen in the central nervous system and the liver. The changes in the central nervous system consisted of a mild cellular infiltration of the meninges over multiple areas of the cortex and also over the brain stem (Fig. 7). The cells consisted of mononuclear cells with occasional polymorphonuclear neutrophils. The brain showed necrosis with cellular reaction in multiple areas. The most striking changes were present in the pons, where there was a diffuse mild perivascular cuffing of the capillaries and arterioles by cells similar to those seen in the subarachnoid space. In addition, the section of pons showed several small foci of

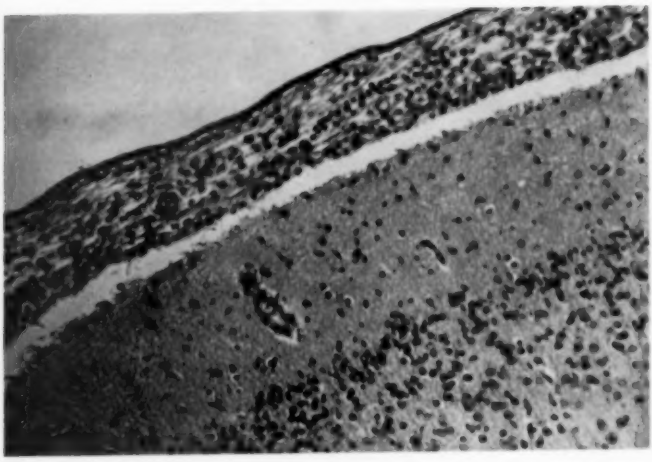


Fig. 7 (Case 3).—Medium-power photomicrograph of the cerebral cortex, showing the mild mononuclear cellular infiltration of the meninges.

necrosis of ganglion cells, glia, and brain substance associated with a cellular reaction consisting predominantly of polymorphonuclear neutrophils and smaller numbers of mononuclear cells (Fig. 8). The nucleus of the troclear nerve showed degeneration of the motor neurons, Fig. 8, with only mild to minimal cellular reaction. Extensive search was made for Toxoplasma organisms and inclusion bodies of the cytomegalic inclusion type and herpes virus type, but none were found. Changes similar to those seen in the pons were present in the basal ganglia, particularly in the periventricular area, where the most marked degree of perivascular cellular cuffing was present. Foci of necrosis were also seen there adjacent to the area of perivascular inflammatory-cell infiltration. The medulla, likewise, showed foci of necrosis and inflammatory-cell infiltration, particularly in the olivary nucleus. Sections of the cortex, choroid plexus, hippocampus, cerebellum, and pituitary were otherwise not remarkable.

The liver showed diffuse necrosis of the parenchymal cells without significant inflammatory-cell infiltration (Fig. 9). There was complete loss of its architecture, with necrosis extending throughout the lobule, leaving only a thin rim of moderately intact parenchymal cells around the portal veins and occasionally around the central veins. A search for evidences of specific etiology, including Toxoplasma organisms, cytomegalic inclusion disease, and herpes virus inclusions in this area was fruitless. The adrenal was of interest because of diffuse necrosis of the fetal cortex with secondary polymorphonuclear-inflammatory-cell reaction. The primordial adult cortex, in contrast, showed little or no change. A further finding was diffuse areas of necrosis of hemopoietic tissue within the medullary spaces of the bone sections both in the verte-

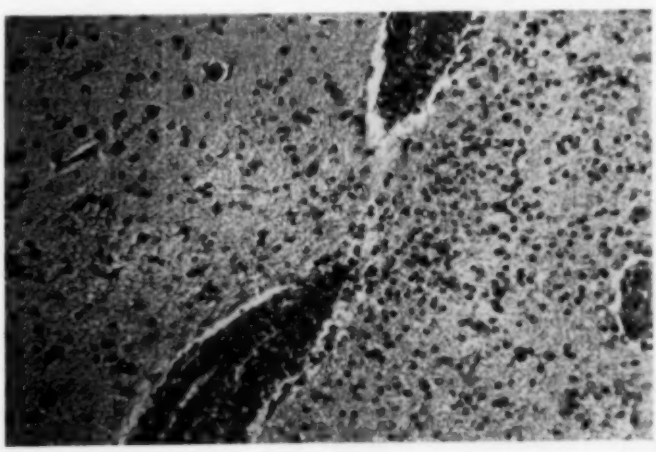


Fig. 8 (Case 3).—Medium-power photomicrograph of pons. Note the necrosis of the ganglion cells, and note the glia with marked mononuclear cellular infiltration of the involved area. The two capillaries in the area show severe perivascular "cuffing" by similar cells.

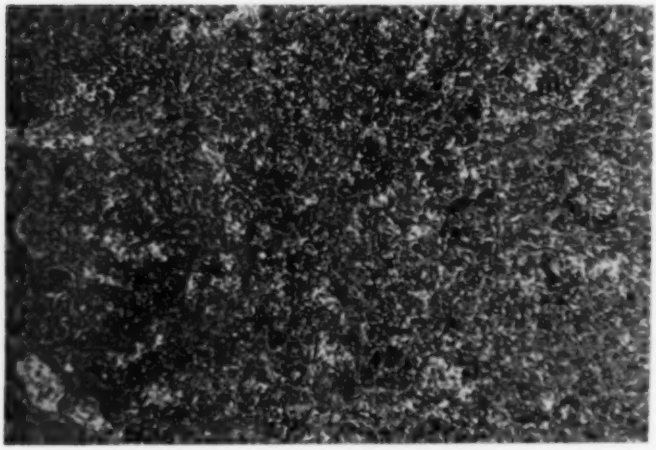


Fig. 9 (Case 3).—Medium-power photomicrograph of liver, showing the extensive degree of necrosis of the parenchymal cells of the liver, without inflammatory cellular infiltration.

bral bodies and in the ribs in the region of the costochondral junctions. The gastrointestinal tract was examined for evidence of peritonitis; only in the pylorus was there a mild serosal infiltrate with polymorphonuclear neutrophils. Elsewhere, the serosal surfaces showed no inflammatory change. The spleen, kidney, thymus, lymph nodes, and thyroid showed no significant change. The umbilical cord showed an acute purulent inflammation extending down into subcutaneous tissue.

Case Summary

A 6-day-old boy had been treated as a premature infant with mild erythroblastosis and possible sepsis. The clinical and serological findings pointed to an extremely minor degree of isoimmunization. At autopsy an E. coli organism was cultured from the blood and ascitic fluid but only minimal inflammatory changes were seen on the serosal surfaces of the bowel. The striking changes were found in the brain and liver, where diffuse meningoencephalitis and severe focal hepatic necrosis were seen. The mother was incubating pleurodynia at delivery and developed symptoms 24 hours post partum. We feel that it is reasonable to postulate that the brain and liver changes were produced by a Coxsackie group B virus infection.

Case 4.—A 5-year-old boy was considered to be in good health until two weeks prior to his admission to a hospital in another city. His illness began with symptoms of an upper respiratory infection. Vomiting and diarrhea occurred several days later. These symptoms continued for several days. Two weeks after the onset of illness, grunting respirations and shortness of breath were observed. At the time of his hospitalization he was found to have an enlarged heart and evidence of cardiac decompensation. Laboratory data revealed hemoglobin to be 11.5 gm. per 100 cu. mm.; WBC, 18,000 cells per cubic millimeter, with 66% neutrophils, 10% juveniles, and 24% lymphocytes. Urinalysis was not abnormal. A roentgenogram of the chest revealed a grossly enlarged heart with no evidence of pneumonic infiltration.

The cause of the cardiac failure was undetermined. Full digitalization and antibiotics produced improvement. Two weeks later medication was discontinued and the patient was discharged from the hospital.

Approximately one week after discharge he was readmitted to the hospital with the same symptoms and physical findings. Laboratory data were as follows: hemoglobin 11 gm. per 100 cu. mm.; WBC 15,400 cells per cubic millimeter, with 57% neutrophils, 6% juveniles, 34% lymphocytes, 2% monocytes, and 1% eosinophils; antistreptolysin titer 80 Todd Units; urinalysis negative. A roentgenogram of the chest again revealed a markedly enlarged heart. At this time the patient was transferred to the Columbus Children's Hospital.

On admission, Dec. 21, 1956, he was observed to be a well-nourished and well-developed 5-year-old boy who appeared pale, apprehensive, and acutely ill. His admission temperature was 101.4 F; the pulse rate, 120 per minute, and respirations, 40 per minute. His blood pressure was recorded as 118/60 mm. of mercury. There was slight injection of the pharynx. Fine rales were heard in the bases of both lungs. The liver was enlarged to 8 cm. below the right costal margin, and the spleen tip was palpable. There was no demonstrable peripheral edema. The neck veins were dis-

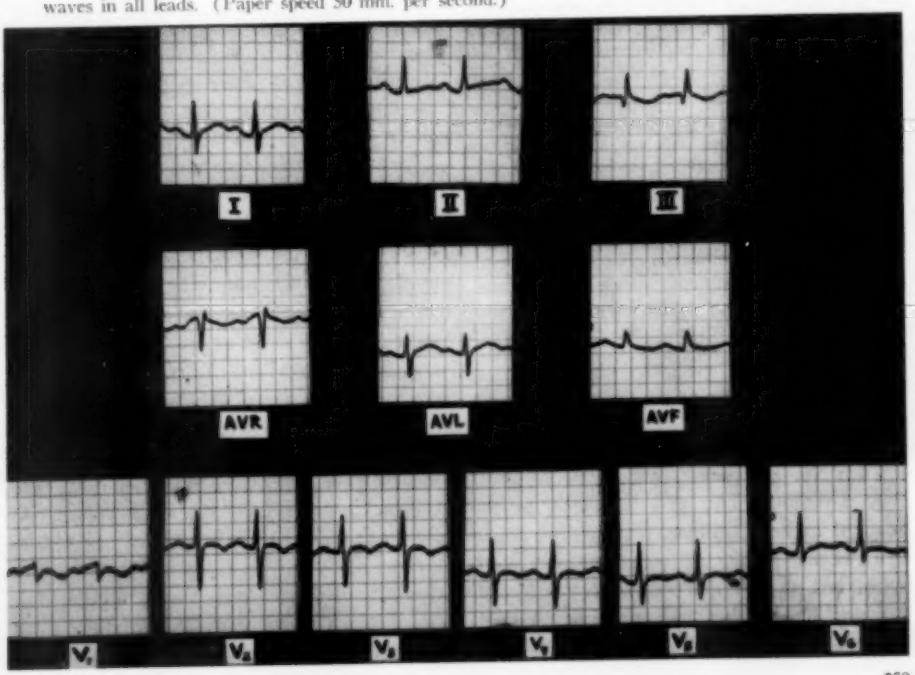
Fig. 10 (Case 4).—Roentgenogram taken on admission, showing gross cardiac enlargement with pulmonary edema and small amount of fluid in the left base.

tended. The heart was enlarged to percussion to the anterior axillary line. The heart tones were distant and muffled, but no murmurs or rubs were detected.

A roentgenogram of the chest showed gross cardiac enlargement with a small amount of fluid in the left base. There was evidence of pulmonary edema (Fig. 10). An electrocardiogram demonstrated a rate of 120 per minute, a P-R interval of 0.14 second, a QRS of 0.06 second, and a QTc of 0.43 second. The T-waves were flat or inverted in all leads, suggesting myocardial and/or pericardial disease (Fig. 11).

The following laboratory data were obtained on admission: Hemoglobin was 9.8 gm. per 100 cu. mm. The white blood cell count was 13,200 cells per cubic millimeter, with 65% neutrophils, 28% lymphocytes, 5% monocytes, and 2% eosinophils. Urinalysis was negative. A culture of the pharynx grew out viridans Streptococcus. The sedimentation rate (Wintrobe) was 40 mm. in one hour. A 3+ C-reactive protein value was obtained. The antistreptokinase titer registered less than 1:10, and the antistreptolysin O titer was 1:50. Febrile agglutinations for typhoid, paratyphoid, Brucella abortus, and Proteus OX19 were negative. A blood culture remained sterile. Skin tests for histoplasmosis, toxoplasmosis, and tuberculosis were negative. The unabsorbed serum agglutinated sheep red blood cells in the titer of 1:128. Blood urea nitrogen was 11 mg. %; cephalin flocculation, 2+; plasma prothrombin, 100%; total protein, 8 gm. per 100 cc., with albumin 3.4 gm. per 100 cc. and globulin 4.6 gm. per 100 cc. Stool cultures for enteric pathogens were negative.

Fig. 11 (Case 4).—Electrocardiogram taken on admission, showing the flat or inverted T-waves in all leads. (Paper speed 50 mm. per second.)



Stool specimens were sent to the Ohio Department of Health Laboratories for viral studies. Coxsackie Group B Type 2 virus was isolated in monkey kidney tissue cultures from feces collected 12 days after admission to this hospital. Serum collected on the seventh day after admission had an antibody titer of 1:10 when tested against 1000 TCD_{50} of the patient's own virus strain. A serum sample which was collected on the 14th day after admission had a titer of 1:50.

Hospital Course

On admission to the hospital, the child was placed in an oxygen tent, digitalization was begun, and a mercurial diuretic was administered. Tetracycline was given by mouth in the dosage of 125 mg. every six hours; his general condition did not improve. Three days after admission a roentgenogram of the chest revealed the heart to be enlarged to the same degree as at the time of admission.

On the fourth hospital day, in view of the failure to improve and a possible existence of a nonspecific inflammatory reaction of the myocardium, as seen in rheumatic carditis, prednisone (Meticorten) was given, 25 mg. every eight hours. During the next four days he improved dramatically and the heart receded in size. The quality of the heart tones improved materially. Laboratory data at this time showed a white blood cell count of 15,500 cells per cubic millimeter, with a normal differential count; a sedimentation rate of 7 mm. in one hour, and a negative C-reactive protein value. With continued improvement, he was discharged on the 18th hospital day, taking a maintenance dose of digitalis and instructed to reduce prednisone dosage during the following month.

He did well at home, and one month after discharge the digitalis and prednisone were discontinued. However, his condition thereafter deteriorated, and it became necessary to readmit him to the hospital because of heart failure. Digitalization again resulted in improvement of his cardiac status. An antibody titer for homologous virus at this time was again 1:50. He remained in the hospital eight days and was discharged with prescription of a maintenance dose of digitalis, improved.

Cardiac enlargement persisted for approximately 10 months, at which time he appeared to have recovered completely.

Case Summary

A 5-year-old boy was admitted to the hospital in heart failure. His illness began five weeks prior to his admission with symptoms of an upper respiratory infection followed by diarrhea and vomiting. A Coxsackie Group B Type 2 virus was isolated in monkey kidney tissue cultures from the feces. Serum tested for neutralizing antibodies against the patient's own virus strain showed a fivefold rise. Digitalis and cortisone produced improvement. Cardiac enlargement persisted for 10 months. He has recovered completely.

Comment

Evidences are accumulating that Group B Coxsackie virus can cause fatal myocarditis in the neonatal period.[1-5] Five reports have cited 10 instances of fatal myocarditis in this age group. In 1955 Montgomery, Gear, et al.[1] reported an outbreak of acute febrile illness in three newborn infants in a Southern Rhodesian maternity home. One of them died on the 12th day after birth, and the other two recovered after being ill for about a week. Group B Coxsackie virus Type 4 was isolated from the feces of the child who died and one of the two who lived. In 1956 Javett et al.[2] reported a similar epidemic in a maternity home in Johannesburg during a local epidemic of pleurodynia and aseptic meningitis in 1952. When the third infant to die was found to have myocarditis, virus isolation studies were performed on the myocardium of the next two fatal cases. Both yielded a Coxsackie Group B Type 3 virus, and the same virus was recovered from the feces of two infants who recovered.

Later in 1956 van Creveld and DeJager[3] reported death due to myocarditis in four newborn infants occurring during a two-month epidemic of "summer grippe" in Amsterdam in 1955. Verlinde, van Tongeren, and Kret[4] described the virus studies done on these four cases and mentioned a fifth case of a newborn infant whose myocardium yielded the same virus. These authors were the first to report isolation of Group B Coxsackie virus from the myocardium. All five of these infants showed Coxsackie Group B Type 4 in their myocardium, and this organism was also found in the brain of one. In November, 1956, Kibrick and Benirschke[5] reported the only instances of

Coxsackie B group virus causing fatal myocarditis in newborn infants in this country. Type 3 Group B Coxsackie virus was isolated from the thoracic cord of one newborn infant, and a Group B Type 4 virus, from the myocardium of a second infant in the area, but the mother of the first infant had a respiratory infection two days before delivery. Twenty-one days post partum her serum showed a neutralizing antibody against the virus isolated from her child in a titer approximately 10 times that prevalent in the community.

Kagan,[6] in reporting a child with pericarditis associated with Group B Coxsackie virus, mentioned that the same virus was isolated from the myocardium of two children, but he did not give any clinical data.

Our Cases 1 and 2 add the 11th and 12th infants reported to die with myocarditis associated with Group B Coxsackie virus. These children are of further interest for two reasons. Case 1 was 7 weeks of age and is the oldest child to die of proven Coxsackie virus myocarditis. Of the 12 cases now reported, clinical data are available in 10. Six of these infants died between the ages of 7 and 9 days; three died at 2, 3, and 4 weeks, respectively. The occurrence of fatal Coxsackie viral myocarditis at 7 weeks of age suggests that death may occur in older children, even beyond this age. This will be discussed below.

Secondly, Case 2 shows that Coxsackie Group B Type 4 virus may produce more than "aseptic myocarditis." From the evidence presented we conclude that it can cause a systemic infection involving the central nervous system, liver, adrenal, and perhaps kidney and lung. Table 2 shows the incidence of organ involvement of the reported cases. Not only is there involvement of the central nervous system in 50% of the infants, but 33% show changes in the liver consistent with those produced by other viruses, and there is involvement of the adrenal in 16%. This extracardiac pathology points to a pathologic process with systemic involvement similar to that seen in infants dying because of systemic herpes simplex or salivary gland virus infection. It

TABLE 1.—*Fatal Cases of Coxsackie Infection*

Case	Date of Report	Authors	Age of Onset	Duration	Epidemic, Local Circumstances, Etc.
1	6/55	Montgomery, et al.	5 days	10 days	Epidemic, acute febrile illness, Maternity Home, S. Rhodesia, S. A., 2-3/54
2	1/56	Javett et al.	9 days	4 hr.	Epidemic, Maternity Home, Johannesburg, S. A., during local epidemic, Bornholm's disease & aspetic meningitis, 1952
3	1/56	Javett et al.	18 days	24 hr.	
4	7-8/56	van Creveld & DeJager	1 day	7 days	Epidemic, "summer grippe," Amsterdam, 1955
5	7-8/56	van Creveld & DeJager	8 days	1 day	
6	7-8/56	van Creveld & DeJager	3 wk.	1 wk.	
7	7-8/56	van Creveld & DeJager	7 days	1 hr.	
8	7-8/56	Verlinde, van Tongeren, & Kret	No data	No data	
9	11/56	Kibrick & Benirschke	3 days	4 days	Probably prenatal infection from mother
10	11/56	Kibrick & Benirschke	No data	No data	No data
11	11/56	Newton & Hosier	6 wk.	10 days	No local epidemic
12	11/56	Newton & Hosier	7 days	1 day	No local epidemic

TABLE 2.—*Organ Involvement in Fatal Cases*

Case	Myocardium	CNS	Liver	Adrenal	Other
1	X			X	
2	X				
3	X	X			
4	X	X	X		Interstitial pneumonia
5	X	X	Central necrosis		Interstitial infilt., kidney
6	X	X	X		
7	X	0			
8	No data available				
9	X	X			
10	No data available				Spleen, 0
11	X	0	0	0	
12	X	X	X	X	

should be pointed out that the infant described in Case 2 in our report initially presented the clinical problem of jaundice and sepsis of undetermined etiology, without suspicion of carditis. Later, a bleeding syndrome was suspected, and her prothrombin activity was found to be reduced, probably as a result of liver damage demonstrated at autopsy. The meningoencephalitis, likewise, was unsuspected and simply contributed to the clinical picture of sepsis. The cause of death of this child does not appear to be cardiac failure alone but rather a combination of the cardiac, liver, brain, and adrenal, and perhaps other organ involvement.

Case 3, included in this report in order to give evidence of multiple organ involvement, presents a newborn infant with probable fatal Coxsackie virus infection. It is unfortunate that viral isolation studies were not performed on this child. At the time of his death, we were not aware of the possibility that Coxsackie virus could produce death in this age group; consequently, no studies were done. Our thinking was later directed toward a possible Coxsackie infection of this infant, since the changes in the brain and meninges resembled those seen in Case 2 and in those cases described by others (van Creveld, Kibrick, and others). The liver necrosis in this child had the pattern of a virus-induced lesion and also resembled the liver changes in Case 2. Necrosis of the bone marrow and fetal cortex has not been described previously in fatal Coxsackie virus infection but has been seen in fatal disseminated herpes simplex in the newborn period. It is of considerable interest that there was no demonstrable myocardial degeneration or inflammation. The cause of death is interpreted to be the severe meningoencephalitis and acute hepatic necrosis. It is very unlikely that this pathologic picture resulted from E. coli septicemia, and there appears to be no reason to postulate that the minimal Rh sensitization of the mother was of much significance in this child's death.

TABLE 3.—*Coxsackie Virus Isolated in Fatal Cases*

Case	Myocardium	CNS	Liver	Adrenal	Kidney	Feces
1		0				B-4
2		B-3				
3		B-3				
4	B-4	B-4				
5	B-4					
6	B-4					
7	B-4					
8	B-4					
9		B-3				
10	B-4		0			
11	B-4					
12	B-4	B-4	B-4		B-4	

Saphir,[7] long recognized as one of the world's authorities in the subject of myocarditis, recently emphasized the apparent increasing incidence of myocarditis in infants. He presented data from five infants dying with diffuse myocarditis. Three of these died in the newborn period, and the

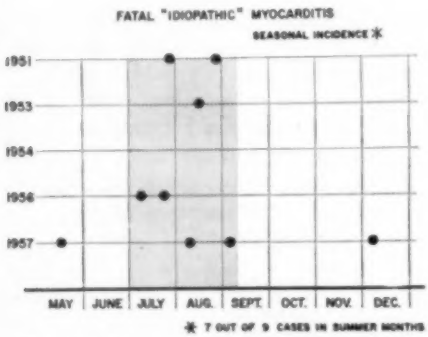


Fig. 12.—Seasonal incidence of myocarditis in children, autopsy material from the Children's Hospital, Columbus, Ohio, for years 1951 through 1957.

others at 9 and 12 months, respectively. He felt that these cases represented instances of viral myocarditis. His Case 1 was an 11-day-old Negro girl who presented the problem of bleeding associated with thrombocytopenia, hypoprothrombinemia, and who died after a four-day illness. Autopsy revealed not only diffuse interstitial myocarditis but also encephalitis, hepatitis, focal pancreatic necrosis, and interstitial pneumonia. A second 11-day-old girl died of cardiac failure of two days' duration and was found to have hepatitis and interstitial pneumonia in addition to her diffuse interstitial myocarditis. A third child died suddenly at 7 days of age and showed scattered histiocytes and polymorphonuclear neutrophils in the periportal spaces of the liver and thymus, in addition to her myocarditis. The brain was not examined. The two older infants did not show significant extracardiac pathology. The brain was not examined in one instance.

In reviewing this material, Saphir felt that these infants had virus-induced myocarditis and postulated that the three dying in the neonatal period had a Coxsackie virus infection. If so, these infants also demonstrates the extracardiac involvement described above, and, in addition, there was focal pancreatic necrosis and inflammation in one infant.

In discussing these cases and their relationship to isolated (Fiedler's) myocarditis, Saphir felt that this group of patients had virus-induced myocarditis, on the basis of morphologic criteria, and were to be differentiated from cases of isolated myocarditis. He felt that the predominant finding in isolated myocarditis was interstitial inflammation, while in virus myocarditis necrosis of muscle fibers seemed to predominate.

This prompted us to review our cases of myocarditis.

In the seven-year period of 1951 through 1957, we have studied at autopsy nine infants and children with myocarditis of varying severity, an incidence of 0.7% of the total number of autopsies performed during this time. With the exception of isolation of Coxsackie virus from the myocardium of two of these, no known cause was found for the myocarditis.

Several features of this case material are of interest. With two exceptions, all children in this group died during the summer months (Fig. 12). These data strongly suggest an infectious etiology of these cases and an infection that is prevalent during the summer months of certain years.

The ages of these children varied from 14 days to 10 years, but they were below 18 months in seven of the nine (Fig. 13).

The morbid anatomy of these hearts was studied in reference to the type and degree of changes present and also to the relation of these changes to the extracardiac pathology observed. In general, the changes in the hearts were limited to the myocardium and

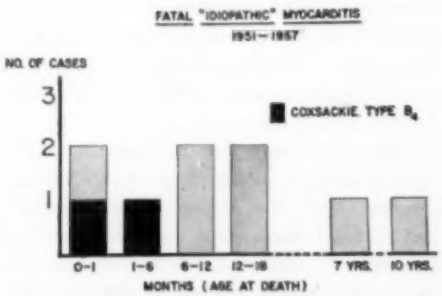


Fig. 13.—Age incidence of myocarditis in children, taken from the Children's Hospital, Columbus, Ohio, for years 1951 through 1957.

TABLE 4.—*Idiopathic Myocarditis: Incidence and Degree of Involvement of Organs Other Than the Heart*

Case	Incidence and Degree of Involvement		
	Myocarditis	Meningoencephalitis	Hepatic Necrosis
1	+++	+	0
2	+++	0	0
3	+++*	0	0
4	+++	0	0
5	++	0	++
6	++	±	++
7	+	0	+++
8	+	+++	±
9	+*	++	+++
10†	0	++	++++

* Coxsackie Group B Type 4 isolated.
† Maternal pleurodynia 24 hours post partum.

consisted of focal necrosis of the muscle bundles with secondary inflammatory cellular reaction. In all but one, the degree of cellular infiltration paralleled the amount of myocardial necrosis. The infiltration of cells varied somewhat, but, for the most part, the dominant cell was mononuclear, with few polymorphonuclear neutrophils present. The pattern of the histopathology in the hearts that contained Coxsackie virus was indistinguishable from that of the other hearts.

Extracardiac involvement is also of interest. Two areas outside the heart showed a significant incidence of pathologic change in these children with myocarditis, namely, the brain and the liver (Table 4).

Four of the nine showed a mild to severe meningoencephalitis which followed a similar distribution. In general, these children had a mild diffuse cellular infiltration of the meninges, chiefly mononuclear in type, together with focal necrotizing encephalitis. The latter was seen largely in the pons, medulla, hippocampus, and, occasionally, choroid plexus.

Four of the nine had moderate to severe hepatic necrosis, with little or no cellular reaction. The distribution of the necrosis was centrilobular in most, but some showed an irregular pattern of focal necrosis. In most instances the picture in the liver was that of central ischemic necrosis similar to that seen in patients dying with peripheral vascular collapse. It is of interest to note, however, that the children who showed the hepatic changes had only mild to moderate changes in the myocardium, while those showing marked myocardial damage showed no liver damage histologically. This suggests that there probably are other factors involved in the pathogenesis of this liver lesion besides cardiac insufficiency.

We included in the graph the data from Case 3. It is of further interest that this infant, who died at the age of 6 days, and whose mother developed typical pleurodynia within 24 hours after this delivery, had severe liver changes similar to those described above. It seems that this type of liver damage can occur without anatomic myocardial involvement. In addition, there was moderate meningoencephalitis.

In view of the presence of the Coxsackie virus in the kidney of Case 2, we searched for evidences of renal damage in the sections of the nine infants with myocarditis, but none was found.

Necrosis of organs outside the heart were seen in two children with myocarditis. One showed focal changes in the spleen; another, in the adrenal (Case 2). Focal necrosis of the medullary spaces of bone marrow was seen in Case 3. No necrosis of lymph nodes was seen.

It does not appear that Coxsackie Group B myocarditis is necessarily a fatal disease. In two reports [1,2] there have been reported six infants suspected of having Coxsackie myocarditis who have recovered. These infants were seen during an epidemic of fatal myocarditis in newborn infants. In one instance a Coxsackie Group B virus was isolated from the feces during the acute phase of the disease, and in two other infants a feces suspension inoculated into suckling mice produced Coxsackie Group B-type lesions. Kagan and Bernkopf [6] also allude to instances of suspected Coxsackie Group B myocarditis in infants and children recovering from the disease.

The clinical findings suggesting the disease are those of a myocarditis from any

cause with bradycardia or tachycardia, a gallop rhythm, cardiomegaly, dyspnea, occasionally cyanosis, a soft apical murmur, or poor heart tones. Other findings of cardiac failure may be present. The electrocardiogram generally shows flattening or inversion of the T-waves or low voltage in all leads.

It is reasonable to assume that Coxsackie myocarditis can also occur in the older child and adult. Cardiac involvement has long been described in cases of pleurodynia in children and adults.[8,9] Acute pericarditis has been the lesion most frequently described. In the past, however, the diagnosis has been made on clinical grounds, without isolation of the virus from the patients. Recently two patients have been reported,[6,10] aged 10 months and 28 years, who have recovered from pericarditis associated with serological evidence of a Coxsackie Group B infection. In one instance a Coxsackie Group B Type 4 virus was isolated from the pericardial fluid.[6] In both patients, involvement of the myocardium was suspected. It has been suggested by van Creveld[11] that the scarring seen in the myocardium of children and young adults dying with cardiac failure may be the residual effects of Coxsackie myocarditis.

Case 4 is presented as an example of a nonfatal Coxsackie Group B Type 2 myocarditis in a 5-year-old child. There may well have been pericardial involvement in this patient, but the clinical findings did not suggest that there was a significant amount of pericardial fluid present. The clinical findings and response to digitalis indicated that the disease was one of the myocardium. Proof of the etiology of the myocarditis depended on an exclusion diagnosis from the laboratory data obtained. In view of the minimal febrile response and negative bacterial cultures, a bacterial etiology did not seem probable. The significance of the positive heterophile test was not clear; probably it was not significant. The symptomatology and course of the disease were not typical of infectious mononucleosis, and no changes were seen in the lymphocytes in the peripheral blood. Hoagland,[12] in a series of 100 patients with infectious mononucleosis, found only minor electrocardiographic changes. He stated that there is no reason to fear serious cardiac involvement in mononucleosis. Rheumatic fever with carditis would seem to be eliminated by the lack of usual symptoms and the negative serological titers for Streptococcus sensitivity.

The possibility of this child being a healthy carrier of the virus, with no direct relationship between his illness and the isolation of the virus from the feces, also had to be considered. McLean et al.,[13] in their report of Coxsackie and ECHO virus infections in Ohio during 1956, showed that the Coxsackie Group B Type 2 virus was not a prevalent virus in the community at the time this child became ill. There was no evidence of spread of infection, as other members of the family deny illnesses of any type. This is refuted, since the virus was isolated and the antibody titers rose during the patient's illness. This is strong evidence to support the thesis that he was not a healthy carrier and that his illness was due to the Coxsackie Group B Type 2 virus. However, even this rise in antibody titer is equivocal, as the first titer (1:10) was performed on serum drawn in the sixth week of illness and the second titer (1:50) was obtained on serum drawn on the seventh week.

Clinically it appears that cortisone played a significant role in the child's improvement during the acute phase of the disease. Javett et al.[2] as well as Kagan and Bernkopf[6] allude to the use of cortisone in patients recovering from cardiac involvement due to Coxsackie Group B virus. No suggestion as to its possible role in the recovery of the patients was given. Kilbourne[14] has shown that the administration of cortisone to adult mice infected with Group B Type 3 Coxsackie virus resulted in extensive and disseminated myocardial necrosis. The individual administration of the Coxsackie virus or of cortisone resulted

in only minimal and inconsistent focal necrosis rarely evident on gross inspection. It should be noted, however, that the amount of cortisone given in these experiments was greatly in excess of the amount given to humans on a surface area basis. On what basis the cortisone contributed to the patient's recovery is not known.

Summary

The isolation is reported of a Coxsackie Group B Type 4 virus at autopsy from the myocardium of a 7-week-old infant who died with heart failure during a nonepidemic period and from the myocardium, liver, lung, and kidney of a 14-day-old infant who died of sepsis of unknown cause.

A third infant, who died at 6 days of age, is included in this report, although no virus isolation studies were performed. The infant's mother, however, was incubating pleurodynia at the time of delivery and developed the typical clinical findings 24 hours post partum. The infant's myocardium showed no morphologic changes, but diffuse meningoencephalitis, severe focal hepatic necrosis, necrosis of the entire fetal cortex of the adrenal, and focal necrosis of the bone marrow were found at autopsy.

A 5-year-old boy recovered from myocarditis during the acute phase of which a Group B Type 2 Coxsackie virus was isolated from the stool and a subsequent rise of homologous serum neutralizing antibodies was demonstrated.

A review of our autopsy experience of myocarditis from 1951 through 1957 showed two features of interest. First, all but two of the nine infants and children died during the summer months. Second, a significant incidence of meningoencephalitis and hepatic necrosis was found.

Dr. Warren E. Wheeler guided and assisted our work on this project; Miss Brenda Olson prepared the graphic illustrations, and Mr. Gillford Millard prepared the photomicrographs.

Children's Hospital (5) (Dr. Newton).

Addendum

In addition to the cases reported, a 6-month-old infant was recently admitted to the hospital with evidence of myocarditis. A Coxsackie virus Group A Type 9 was isolated from feces, but the acute- and convalescent-phase sera were lost en route to the reference laboratory. The infant has improved but is not completely well.

In a recent report of interest, Movitt et al.[15] reported two patients with acute benign pericarditis due to Coxsackie viruses. In both patients a Coxsackie virus was isolated from stool specimens. In one the Coxsackie virus was identified as Group B Type 3, and in the other, Group A Type 1.

REFERENCES

1. Montgomery, J.; Gear, J.; Prinsloo, F. R.; Kahn, M., and Kirsch, Z. G.: Myocarditis of the Newborn: Outbreak in Maternity Home in Southern Rhodesia Associated with Coxsackie Group B Virus Infection, South African M. J. 29:608-612, 1955.

2. Javett, S. N., et al.: Myocarditis in the Newborn Infant: A Study of an Outbreak Associated with Coxsackie Group B Virus Infection in a Maternity Home in Johannesburg, J. Pediat. 48: 1-22, 1956.

3. van Creveld, S., and DeJager, H.: Myocarditis in Newborns, Caused by Coxsackie Virus: Clinical and Pathological Data, Ann. paediat. 187: 100-112, 1956.

4. Verlinde, J. D.; van Tongeren, H. A. E., and Kret, A.: Myocarditis in Newborns Due to Group B Coxsackie Virus: Virus Studies, Ann. paediat. 187:113-118, 1956.

5. Kibrick, S., and Benirschke, K.: Acute Aseptic Myocarditis and Meningoencephalitis in the Newborn Child Infected with Coxsackie Virus Group B Type 3, New England J. Med. 255:883-889, 1956.

6. Kagan, H., and Bernkopf, H.: Pericarditis Caused by Coxsackie Virus B, Ann. paediat. 189: 44-50, 1957.

7. Saphir, O., and Cohen, N. A.: Myocarditis in Infancy, A. M. A. Arch. Path. 64:446-456, 1957.

8. Bing, H. I.: Epidemic Pericarditis, Acta med. scandinav. 80:29-33, 1933.

9. Heckscher, H.: Myositis Epidemica Serositis, Acta med. scandinav. 80:251-261, 1933.

10. Weinstein, S.: Acute Benign Pericarditis Associated with Coxsackie Virus Group B Type 5, New England J. Med. 257:265-267, 1957.

11. van Creveld, S.: Virus Myocarditis in Infancy: Acute Phase and Possible Late Sequelae, presented at Symposium on Viral Infections in Infancy and Childhood, New York Academy of Medicine, New York, March 13, 1958.

12. Hoagland, R.: Cardiac Evolvement in Infectious Mononucleosis, Am. J. M. Sc. 232:252-257, 1956.

13. McLean, D. M.; Croft, C. C.; Prince, J. T., and Heckmann, E. E.: Coxsackie and ECHO Virus Infections in Ohio During 1956, Ohio M. J. 53: 907-909, 1957.

14. Kilbourne, E. D.; Wilson, C. B., and Perrier, D.: The Induction of Gross Myocardial Lesions by a Coxsackie (Pleurodynia) Virus and Cortisone, J. Clin. Invest. 35:362-370, 1956.

15. Movitt, E. R.; Lennette, E. H.; Mangum, J. F.; Berk, M., and Bowman, M. S.: Acute Benign Pericarditis: Report of 2 Cases Associated with Group A and Group B Coxsackie Viruses, New England J. Med. 258:1082-1086, 1958.

Fetal Ascites

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Extensive ascites at birth is uncommon, and only 107 cases have been reported. The ascites may be due to several widely differing causes, but in almost all cases the children having this condition have died. We wish to report an infant with marked fetal ascites who was treated conservatively and subsequently had an uneventful course.

Report of a Case

A boy was the third child of a 22-year-old Spanish-American woman whose blood was Type A, Rh-positive. She had had regular prenatal care, and the pregnancy had been uneventful except for the "grippe" during the first month of pregnancy and marked enlargement of the abdomen in the third trimester. Roentgenograms taken during the 35th week of pregnancy were interpreted as showing a fetus of normal size and proportions. However, review of these films disclosed less flexion of the fetal thighs on the abdomen than is usually seen, although no definite evidence of ascites could be ascertained.

The infant was born at term after a 10½-hour labor, and delivery was from the mentoanterior position. A left mediolateral episiotomy was performed, but the delivery was difficult because the infant had marked abdominal distention. The infant cried spontaneously but appeared listless and had severe respiratory distress. An endotracheal catheter was passed, without any apparent improvement in the child's condition. Because of marked enlargement of the abdomen an abdominal paracentesis was done in the delivery room, and a total of 360 cc. of clear, straw-colored fluid was removed. This resulted in an immediate and marked improvement in breathing. The infant was catheterized without difficulty, and 7 cc. of normal appearing urine was withdrawn. He was transferred to the nursery, and on admission there he weighed 4390 gm. (9 lb. 10 oz.). Within a few minutes he again began to have respiratory distress and became cyanotic despite the administration of supplemental oxygen. Another abdominal paracentesis was performed, and a No. 18 polyethylene catheter was allowed to remain in the abdominal cavity. Ascitic fluid dripped through the catheter for about 48 hours, at which time the catheter was removed. At the age of 24 hours he weighed 3540 gm. (7 lb. 12 oz), having lost approximately 1200 gm. (2 lb. 10 oz.) during the first day.

Physical examination at the time of admission to the nursery revealed a well-formed infant with massive abdominal distention. Head circumference was 37 cm.; chest circumference, 34 cm., and length, 49 cm. There was moderate molding of the head. Respirations were rapid and shallow, but breath sounds were heard throughout both lung fields. The liver was palpable 3 cm. below the right costal margin, and the edge was smooth and firm. The spleen was not palpable. No unusual venous pattern was evident over the abdomen. There was marked scrotal edema. After paracentesis the kidneys were palpable and appeared normal in size. The remainder of the physical examination was not remarkable.

Penicillin and chloramphenicol were administered for seven days. Feedings were started at the age of 24 hours and were taken well. By the third day of life the scrotal edema had disappeared, and it was noted that the child had bilateral inguinal hernias which were easily reducible. On the fifth day of life the tip of the spleen could be palpated and the edge of the liver was palpated 5 cm. below the right costal margin. After the cessation of abdominal drainage, the infant had an uneventful hospital course, and he was discharged on the 10th day of life, weighing 3760 gm. (8 lb. 4 oz.)

Laboratory Data.—The infant's blood was Type A, Rh-positive. Ascitic fluid: specific Gravity was 1.015; NPN, 25.2 mg. %; total protein, 2.83 gm. %; albumin, 2.54 gm. %; globulin, 0.29 gm. %. Gram stain of the fluid revealed no bacteria and only a rare RBC. The culture was negative. Roentgenograms of the abdomen revealed marked ascites, but no other abnormalities could be seen. An electrocardiogram was interpreted as being normal. The reactions to skin tests for blastomycosis, tuberculosis (first strength P. P. D.), coccidiodomycosis, and histoplasmosis were all negative. Blood findings: RBC, 6,500,000; WBC, 12,850, with 55% segmented neutophils, 19% unsegmented neutrophils, 3% lymphocytes, and 5% monocytes. There were 88 nucleated red cells per 100 white blood cells. The serologic reaction for

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syphilis was negative. Urine (day of birth): yellow; cloudy; acid; albumin, 2+; sugar, negative; sediment, 6 to 8 coarse granular casts per high-power field. Three days later the urine analysis was completely normal. Blood: thymol turbidity, negative; serum glutamic oxaloacetic transaminase (SGOT), 280 units; serum glutamic pyruvate transaminase (SGPT), 100 units; serum protein: total, 4.29 gm. %; albumin, 3.74 gm. %; globulin, 0.55 gm. %.

The infant was seen in the clinic nine days after discharge from the nursery. He had been doing well, was taking his formula hungrily, and had gained 1 lb. 2 oz. He was an alert, active infant. A soft systolic murmur was heard along the left sternal border. The edge of the liver could be palpated 3.5 cm. below the right costal margin. A cystic mass measuring 2×2 cm. was palpated in the epigastrium. It appeared to be attached to the liver and could not be felt when the infant tightened his abdominal muscles. At this time the serum transaminase (SGOT) was 55 units; total proteins, 5.46 gm. %; albumin, 4.36 gm. %; globulin, 1.1 gm. %. The alkaline phosphatase was 14.6 Bessie-Laurie units (normal, 3-7 units). Five weeks later he weighed 7.2 kg. (12 lb. 15 oz.) and the mass in the abdomen could still be palpated.

The child was not seen again until the age of 6 months, at which time he was brought to the emergency room of the University of Colorado Medical Center with a fever of 104 F and was found to have purulent right otitis media, from which β-hemolytic Streptococcus was cultured. He was treated with penicillin given parenterally, with prompt subsidence of the infection. On this occasion the liver was not enlarged and the cystic mass no longer could be felt. At the age of 6½ months SGOT was 62 units; thymol turbidity, 1 Kunkel unit; direct-reacting bilirubin (van den Bergh), 0.1 mg.; indirect-reacting, 0.3 mg.; total protein, 5.7 gm. %; albumin, 3.4 gm. %; globulin, 2.3 gm. %; alkaline phosphatase, 4.3 Bessie-Laurie units.

He was last seen at the age of 7 months, at which time he was doing well.

Comment

Fetal ascites is the term used to describe the collection of clear ascitic fluid unaccompanied by generalized edema that either occurs during intrauterine life or appears shortly after birth. In 1954 France and Back [1] were only able to find 103 recorded cases of fetal ascites in the world literature. These cases plus the 2 that they reported, an additional case reported by Barr and MacVicar [2] and one subsequently described by Minkowski and co-workers [3] bring the total to 107.

In their excellent reviews of the subject of fetal ascites, Dorland [4] and France and Back have discussed the mechanism of production of the fluid and have indicated that fetal peritonitis and gross abnormalities of the urogenital or alimentary system probably are the most important causes but that ascites may also occur with other conditions. The latter include defects in the fetal circulation, compression of the larger abdominal vessels by tumors, cirrhosis, absence of the ductus venosus, syphilis, pressure on the abdominal vessels by an overdistended bladder, agenesis of intra-abdominal organs,[5] imperforate anus, and cardiac failure. Lord [5] has indicated that there is no evidence that either heart failure or obstruction of the portal circulation by a tumor or congenital defect causes pure ascites. In those cases where fetal peritonitis seems to have played some role, the cause of the peritonitis was often obscure but may have been due to a pyogenic or tuberculous infection in the mother or to perforation of the fetal intestine.[6] Congenital obstruction of the lower urinary tract has been a common finding in those instances of fetal ascites where a definite anatomic abnormality was demonstrated, and in these cases the fluid may arise from leakage or transudation through a thin area of bladder wall, from an actual rupture of the bladder, or as a general effect of impaired renal function.

No specific anatomic abnormality was found to account for the ascites in our patient. Except for the "grippe" in the first month of gestation, the pregnancy had been uneventful. Because of marked abdominal distention, the delivery was difficult, and there was severe respiratory distress at birth, which was not relieved until abdominal paracentesis had been performed. An indwelling polyethylene catheter was inserted into the abdomen, with drainage of ascitic fluid for approximately

48 hours. No other specific therapy was carried out, and the subsequent course was uneventful. During the first day the infant lost approximately 1200 gm. (2 lb. 10 oz.). Hepatomegaly was present in the neonatal period, and a cystic mass was palpated in the epigastrium at 3 weeks of age. However, the mass was no longer palpable and the liver was not enlarged at the age of 6 months.

The presence of a large amount of fluid in the abdomen of the fetus may cause an arrest in labor which may be relieved by spontaneous rupture of the abdomen of the fetus or may necessitate operative rupture to complete the delivery. After birth extreme abdominal distension may produce respiratory distress. Occasionally the diagnosis of fetal ascites has been suspected on roentgenograms taken prenatally. In our patient review of the roentgenograms taken during the 35th week of gestation suggested that ascites was present, since the degree of flexion of the thighs on the abdomen was less than is usually found.

The ascitic fluid in cases of true fetal ascites has the characteristics of a transudate. Generally it is clear; is light yellow, green, or brownish-red; contains a few flakes of lymph, has a specific gravity of 1.002 to 1.015, is alkaline in reaction, and contains chlorides, sulfates, phosphates, protein, sugar, and occasionally urea in small amounts. The amount of fluid in the abdomen varies, averaging about 3 to 4 liters, but as much as 15 liters may be present.[6]

Most of the infants reported to have had fetal ascites have died, with death occurring just before, during, or shortly after birth. In his review of 80 cases Dorland could find only 1 case that recovered. Subsequently James and Davis[7] reported survival in an infant who developed ascites at the age of 3 weeks and was found to have an obstruction of the posterior urethra, and Bellin and Bailit[8] described an infant having "portal cirrhosis of the newborn infant associated with maternal infectious hepatitis" who was treated with repeated paracenteses and was alive at the age of 18 months, when paracenteses were no longer necessary.

In the differential diagnosis of fetal ascites it is necessary to consider other conditions where there are marked accumulations of fluid. These include generalized anasarca, congenital polycystic kidney, marked distention of the urinary tract, cystic degeneration of the fetal liver,[4] fluid distention of the genital tract,[4] ovarian cyst, and chylous ascites. The latter is readily differentiated from true fetal ascites by the characteristics of the fluid. Chyle is milky or creamy, is opalescent, is coagulated by the addition of nitric acid but not by heat, contains fat globules, and has a high fat content.

Since fetal ascites may result from a number of dissimilar conditions, it is impossible to make any generalizations as to management. In some cases, conservative therapy limited to repeated paracentesis has been associated with apparent recovery. Where some specific pathologic condition is present, correction of the defect, when possible, is, of course, of paramount importance.

Summary

A case of fetal ascites with recovery following conservative therapy is reported.

The mechanisms that might produce this condition are discussed.

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REFERENCES

1. France, N. E., and Back, E. H.: Neonatal Ascites Associated with Urethral Obstruction, Arch. Dis. Childhood 29:565, 1954.

2. Barr, J. S., and MacVicar, J.: Dystocia Due to Foetal Ascites, J. Obst. & Gynaec. Brit. Emp. 63:890, 1956.

3. Minkowski, A.; Sainte-Anne Dargassies, S.; Armaganidou, D.; Bourgonnier, L.; Hebert-Jouas, C., and Pellerin, D.: Ascite foetale avec hydramnios: Évolution exceptionnelle vers la guérison;

revue critique de la physiopathologie du liquide amniotique, Études néo-natal. 6:25, 1957.

4. Dorland, W. A. N.: Watery Accumulations in the Fetal Abdomen Obstructing Labor, Amer. J. Obst. 79:474, 1919.

5. Lord, J. M.: Foetal Ascites, Arch. Dis. Childhood 28:398, 1953.

6. Hoffman, C.; Sternberg, S. D., and Rascoff, H. D.: Fetal Ascites, A. M. A. Am. J. Dis. Child. 82:28, 1951.

7. James, U., and Davis, J. A.: Congenital Urethral Obstruction Presenting as Ascites in the Newborn Period, Proc. Roy. Soc. Med. 45:401, 1952.

8. Bellin, L. B., and Bailit, I. W.: Congenital Cirrhosis of the Liver Associated with Infectious Hepatitis of Pregnancy, J. Pediat. 40:60, 1952.

9. Tietz, K. G., and Davis, J. B.: Ruptured Ovarian Cyst in a Newborn Infant, J. Pediat. 51: 564, 1957.

Effects of Low-Dose X-Radiation on the Mouse Embryo

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Many investigators have attempted to treat animals during early pregnancy with x-radiation and to examine the effect as manifested by abnormalities in the offspring. Generally the objective has been to clarify factors influencing the development of congenital abnormalities and to ascertain the teratogenic dosages of radiation and compare effects at different developmental stages of embryonic life. Thus, the malformations which have been studied were mostly those that had developed in near-term fetuses or in newly born animals. Where abnormal morphogenesis had occurred early in pregnancy, development had been permitted to go on until the relatively late stages at which animals were killed. Moreover, except for a few investigators, such as Wilson and Karr [1] and Hicks,[2] most others have concentrated on the morphological nature of congenital anomalies and have not concerned themselves with a systematic study of mechanisms leading to maldevelopment. In particular, the mechanisms leading to maldevelopment of the central nervous system by x-radiation are still obscure and constitute a problem requiring further study, and we have been engaged in studies of the processes of maldevelopment caused by various external agents including x-radiations of 150 and 100 r on the eighth day of pregnancy in mice.[3]

Results to date of experiments with x-irradiation of pregnant mice have been inconclusive and even conflicting. On the one hand, Plough [4] has claimed that a single dose as low as 100 r does not cause any gross abnormal development of the mouse embryo, and, on the other hand, Russell,[5] Wilson and Karr,[1] and Hicks [2] incline to the opinion that an x-ray dose as low as 25 r may exert a harmful influence upon embryos when administered during early development. In general, the data are insufficient for reaching a firm conclusion. Our own experiments in which mice were subjected to the action of various agents including x-radiation during early stages of pregnancy suggest that a common pathologic process plays a fundamental role in determining many maldevelopments of the central nervous system; its basis appears to lie in the fact that the cellular elements of the ependymal layer of the central nervous system are especially reactive to many teratogenic agents. Against this background we have also examined the effect of low doses of x-radiations such as 50 and 25 r on the developing tissues of the central nervous system.

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Materials and Methods

Strain of mouse, procedures of breeding, and examination for and determining of pregnancy by the vaginal plug method were the same, except for the diet,* as those used in experiments employing other agents that have been described elsewhere.[6] Whole-body x-radiation was administered in a single dose on the 8th day of pregnancy, and embryos were removed from the

TABLE 1.—*Pregnancy Status of Mice X-Irradiated on the Eighth Day of Pregnancy*

X-Ray Dose, r	X-Rayed Mice, No.	Embryos/ Litter	Normal Embryos,		Abnormal Embryos, Living & Dead		Resorbing & Missing * Embryos		Total Embryos, No.
			No.	%	No.	%	No	%	
150	20	7.05	4	2.8	93	66.0	44	31.2	141
100	20	6.70	25	18.7	81	60.4	28	20.9	134
50	20	7.35	101	68.7	34	23.1	12	8.2	147
25	20	6.90	103	74.7	18	13.0	17	12.3	138
Totals			233		226		101		560
Untreated controls	30	6.93	178	85.6	10	4.8	20	9.6	208

* Includes missing embryos inferred from count of corpora lutea and implantation sites in mice showing no other trace of pregnancy.

uterus and examined as in previous experiments on the 13th day of pregnancy. All specimens were examined grossly, and some were also examined microscopically. X-irradiation was carried out with use of a therapeutic x-ray machine. The beam was that produced by the factors 200 kv., 20 ma., 80 cm., and the filter was 0.5 mm. Al+0.5 mm. Cu, 13.69 r per minute.

TABLE 2.—*315 Malformations of the Central Nervous System in 459 Living and Dead Embryos Examined on the Thirteenth Day After Maternal X-Irradiation on the Eighth Day of Pregnancy*

	Malformations, No.				Untreated Controls
	150 r *	100 r	50 r	25 r	
Telencephalon retarded	5	5	2	0	0
Hydrocephalus	37	35	8	2	0
Brain hernia	29	26	9	0	0
Pseudencephaly	5	4	0	2	0
Flexion of spinal cord	31	24	18	15	9
Hydromyelia	19	10	3	1	0
Hernia of spinal cord	2	0	0	0	0
Distended CNS (died on 10th-12th day)	14	6	3	0	1
Total	142	110	43	20	10

* Dose of x-ray.

Results

Table 1 lists the frequencies, and Table 2, the kinds of grossly detectable malformations † observed after irradiation of the mothers in pregnancy. Table 1 also shows the extent of embryonic loss up to the 13th embryonic day, when the uterine contents were examined. The percentage of embryonic loss in the control group was 9.6%; in the group treated with 50 r it was 8.2%, whereas in the group treated with 25 r it was 12.3%. These results differ significantly from the results obtained in the group treated with 150 r (31.2%) or 100 r (20.9%) and are similar to intrauterine losses observed in controls (9.6%). If dead embryos with anomalies found on the 13th day were included in the number of embryonic loss, in the group treated with 50 r the percentage would rise from 8.2% to 10.2%; in the group treated with 25 r, it remains unchanged (12.3%), and it is almost unchanged among control animals, rising from 9.6% to 10.0%. Thus, there seems to be no lethal effect upon embryos when mothers are irradiated with a dose of 50 r or less.

TABLE 3.—*Other Kinds of Malformations Found in the Same 226 Abnormal Embryos Shown in Table 1 by Type of Malformation*

	Malformations, No.				Untreated Controls
	150 r	100 r	50 r	25 r	
Anophthalmos	7	1	0	0	0
Microphthalmos	14	9	0	0	0
Cleft face	2	0	0	0	0
Median cleft lip	3	1	0	0	0
Unilateral harelip	3	0	0	0	0
Malformed mandible	14	10	1	0	0
Ectopia cordis	8	3	0	0	0
Malformed tail	0	5	0	0	0
Totals	51	29	1	0	0

In the group treated with 50 and 25 r involved the central nervous system with the exception of one specimen with a malformed jaw. Eye abnormalities and other mesodermal defects of the face, thorax, and heart were not found. In the group treated with 50 r abnormalities were mild except for three embryos dead with a "distended central nervous system." [7] Un-

* A solid diet manufactured by Oriental Yeast Manufacturing Co., Ltd., Tokyo.

† Hydrocephalus and hydromyelia are judged only from microscopic examinations.

like malformations found after 150 and 100 r, the defects occurring after 50 and 25 r were not grossly evident. They were of complicated nature in their external appearances (Table 2), except for two pseudencephalies found among progeny of females treated with 25 r during pregnancy.

Malformations Induced by Low Dosages of X-Ray.—Detailed morphologic descriptions of abnormalities observed will be published elsewhere. Here they will be described in brief.

Hydrocephalus: This was observed in 10 fetuses but was only detectable on microscopic examination. No serious cases were seen of embryos lacking ventricular septums with asymmetrical telencephalons, retarded development of the telencephalon, or serious hydromyelia. Such lesions have been found in progeny of mothers x-irradiated with larger doses. In a few cases, however, the wall of the brain mantle facing the lateral ventricle was uneven (Fig. 1).

Brain Hernias: In external appearances, there were no cases which presented distinct brain hernias, and only protuberances of the diencephalon or mesencephalon were seen. Likewise, no cases with configurated tumor-like appearances were seen of the kind that have been observed in mice treated with 150 or 100 r. These specimens of encephalic protuberances are interpreted to represent very slight degrees of brain hernia.

Pseudencephaly: This malformation presents a simple typical appearance similar to that observed after the use of other agents. No cases were found of cleft lip or face or other gross abnormalities that have been described in the group treated with higher doses of x-ray or of thoracic herniations such as ectopia cordis.

Spinal Cord Abnormalities: A flexed spinal cord was a common aftermath of low dose x-irradiation (Table 1); sometimes this was associated with enlargement of the lumen (hydromyelia). The flexions themselves were simple and were localized in the upper limb-level. None manifested rhombic-shaped deformities of the lumen of the

Fig. 1.—Cross section of the right side of the telencephalon of an embryo that had been irradiated with 50 r on the eighth day of gestation. Brain cavities are enlarged to the point of hydrocephalus, and the brain mantle is thinned; the wall facing the lateral ventricle is uneven from proliferation of ependymal elements.

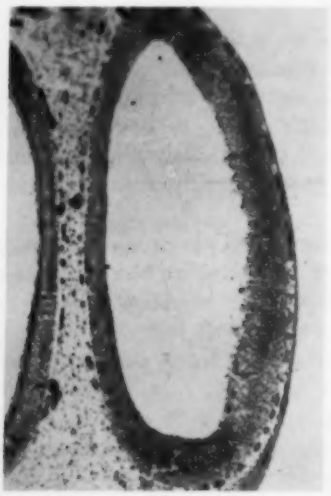
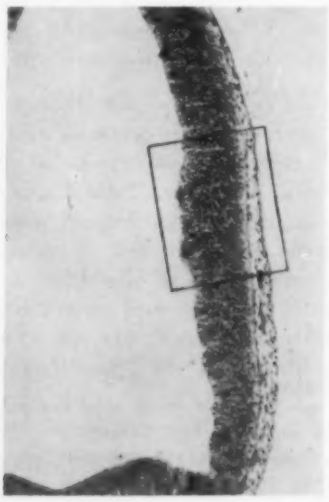


Fig. 2.—Cross section of a part of the mesencephalon of an embryo that had been irradiated with 25 r on the eighth day of gestation. Despite an externally normal appearance, ependymal elevations are seen in parts of the brain mantle facing the third ventricle.



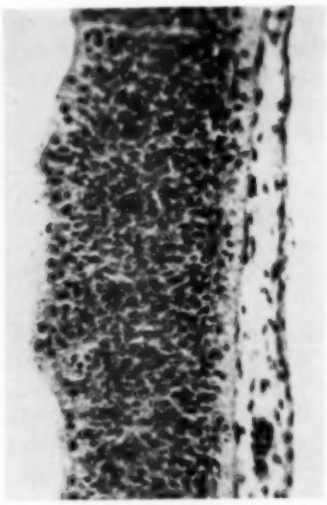


Fig. 3.—One of the elevations shown in Figure 2 is shown at high-power magnification. Proliferation of ependymal cells, many mitotic figures, and irregular arrangement of cells are seen.

Fig. 4.—Cross section of a lower part of the myelencephalon after exposure to 50 r. External appearance is normal, but the wall of the brain facing the fourth ventricle is partially uneven.

spinal cord as were seen after maternal exposure to 150 and 100 r.

Ocular Defects: In the group treated with 50 or 25 r, there were no embryos with microphthalmos or anophthalmos as were seen in groups treated with 150 and 100 r. However, in the group treated with 50 r, among nine embryos there were two with slightly malformed eye-cups (Fig. 7). In those specimens an aberrant arrangement of the cells forming the anlage of the retina was seen.

Fig. 5.—Section of a high-power photomicrograph of the uneven part of the wall shown at the upper right of Figure 4 is presented at a large magnification. Findings similar to those shown in Figure 3 are seen.

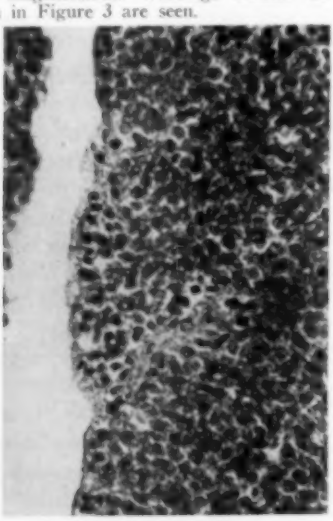


Fig. 6.—Cross section of an embryo with slight flexion of the cervical cord after exposure to 50 r. The lumen of the spinal cord is distended; that is to say, hydromyelia is present.

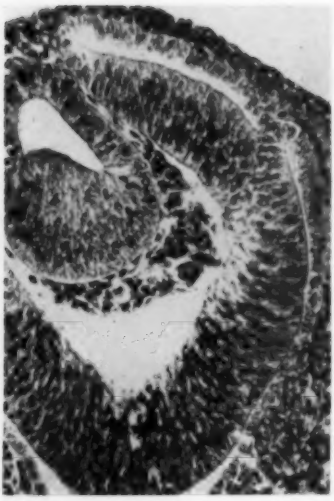


Fig. 7.—Cross section through the left eye of an embryo after exposure to 50 r. This embryo has hernia of the mesencephalon not shown in the photograph. However, the cellular architecture of the primordial retina is patently irregular.

Slight changes of the primordium of the brain and spinal cord were detectable by microscopic examination in 7 embryos among 11 without any gross anomalies which were examined at random in the group treated with 50 r and in 4 among 10 in the group treated with 25 r. These slight changes were observed in the primordium of the telencephalon, myelencephalon, and spinal cord and minor plications of the di- or mesencephalon, together with unevenness of the internal surface facing the brain cavity. Also, partial elevations of the ependyma were impressive, which represent a proliferative process of ependymal cells of irregular distribution (Figs. 1-5). In the involved parts many mitoses and aberrant arrangements of the cells were seen. In contrast to cases treated with 150 and 100 r, no rosettes were seen in the nervous or neighboring tissues.

Comment

Generally speaking, abnormalities caused by x-radiations become more prominent and complicated in appearance with increasing dosage. Conversely, as the dose is progressively reduced the nature of congenital malformations changes. Between maximal and minimal extremes lie exposures to intermediate intensities and transitional forms of defect manifested upon the embryo.

However, a common feature of abnormalities of the central nervous system, whether caused by high doses or low doses of x-ray, is a basic disturbance of the ependymal layer. Moreover, developing parts of the central nervous system appear to have different gradients in their potentiality for maldevelopment just as they have for normal development and the susceptibility varies from level to level. When x-ray dosage is high, even parts with low susceptibility may be extensively involved; presumably this explains why mesodermal tissue may give rise to complex, grossly manifest abnormalities. By contrast, when low doses of x-radiation are employed they will affect the nervous tissues of the embryo only at specific stages of development and where the potentiality for normal development is great. Thus the fact that gross abnormalities such as brain hernia and hydrocephalus were clearly caused by dosages as low as 50 r is interpreted to indicate tissue susceptibility to this maldevelopment. Similarly, the production of spinal curvatures, seen more frequently in test animals than in controls, provides an indication of tissue susceptibility at the cord level.

In evaluating observed differences between the effects of high-dose and low-dose radiation not only the direct effect of this source of energy upon the embryo but also the indirect effect operating via the maternal organism is to be taken into consideration. However Brent's experiments, in which he was able to guard the embryo from gross malformation by lead shielding, indicate that the direct effect of radiation on embryonic tissues plays the really significant role. Moreover, when smaller doses of radiation are used, as in these experiments, it is probable that the relative role of maternal disturbance is even less. On the other hand, the total influence of x-radiation after

whole-body exposure of pregnant mammals upon embryonic development is probably the aggregate of the effects of x-ray injury upon both mother and embryo, and further facts are needed before interrelations can be wholly clarified.

When embryos from mothers treated with low dose (50 or 25 r) x-radiations were examined at random microscopically, small elevations of the ependymal elements facing the primordial brain cavity were seen. These were interpreted to represent proliferations of a type which in "predisposed" regions might result later in gross malformations of the brain—in the production of brain hernias, for example, if they occurred at the top of the mesencephalon. Similarly, the finding is interpreted to represent a minimal change of the kind leading to the development of meningocele, pseudencephaly, or spina bifida. Without microscopic examination such teratogenic effects of low-dose radiation could hardly have been detected. On the other hand, abnormal deviations of microscopic dimensions must be taken into consideration when it comes to reconstructing pathogenesis and in interpreting the pathogenesis of gross deformities of the kind that have been observed to follow x-ray injury of the developing embryo.

Summary and Conclusions

Mice were subjected on the eighth day of pregnancy to whole-body irradiation of 50 and 25 r. The embryos were examined on the 13th day of pregnancy either grossly or in sections.

Abnormal embryos constituted 23.1% of the group treated with 50 r and 13% of the group treated with 25 r. By contrast, abnormal embryos comprised only 4.8% of the embryos in control groups. Dead embryos occurred at approximately the same rates in both treated and control groups.

Evident abnormalities were preponderantly of the central nervous system, except for one specimen of hypognathus which appeared in the group treated with 50 r. No cases of complicated external appearance occurred such as have been observed previously in groups treated with over 100 r. Such differences may result from the smaller doses of x-ray employed, but some effects may derive from maternal injury, since a high dose will damage maternal organs more seriously than a low dose. Also, a synergistic effect is to be considered.

Among embryos without gross abnormalities, specific pathologic changes were found in the brain and spinal cord anlage, indicative of a proliferation of the ependymal elements. Such changes suggesting a serious prognosis were found among embryos examined microscopically on the 13th day of embryonic life.

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REFERENCES

1. Wilson, J. G., and Karr, J.: Effect of Irradiation on Embryonic Development: I. X-Rays on the 10th Day of Gestation in the Rat, Am. J. Anat. 88:1-33, 1951.

2. Hicks, S. P.: Developmental Malformations Produced by Radiation, Am. J. Roentgen. 66:272-293, 1953.

3. Murakami, U.: Experimental Embryologic and Pathologic Study on Malformation of the Central Nervous System, Acta path. japon. 5(Supp.):495-513, 1955.

4. Plough, H. H.: Radiation Tolerances and Genetic Effects, Nucleonics 10:16-20, 1952.

5. Russell, L. B.: Effect of Low Doses of X-Rays on Embryonic Development in the Mouse, Proc. Soc. Exper. Biol. & Med. 95:174-178, 1957.

6. Murakami, U.: Artificial Induction of Pseudencephaly, Short-Tail, Taillessness, Myelencephalic Blebs and Some Fissure Formations (Phenocopies) of the Mouse, Nagoya J. M. Sc. 15:185-194, 1952.

7. Snell, G. D.; Bodemann, E., and Hollander, W.: Translocation in the House Mouse and Its Effect on Development, J. Exper. Zoöl. 67:93-104, 1934.

8. Brent, R. L.: The Indirect Effect of Irradiation on Rat Embryos, A. M. A. J. Dis. Child. 93:7-8, 1957.

Acute Cerebellar Ataxia of Undetermined Origin in Childhood

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When a child, previously well, rapidly develops ataxia one's inclination—and properly so—is to suspect a posterior fossa tumor. However, we wish to direct attention to a syndrome of acute cerebellar ataxia which, as a rule, carries an excellent prognosis. It is characterized by the abrupt occurrence of ataxia, particularly of the trunk and lower extremities; little if any fever; minimal evidences of systemic illness, and practically invariable subsidence of all signs of nervous system disorder in a matter of days to weeks. In general the cerebrospinal fluid is normal, although on some occasions there is a moderate pleocytosis and elevation of protein. Frequently headache, vomiting, irritability, or listlessness precede the ataxia by a few days or may accompany its onset. On the other hand, the ataxia may suddenly make itself evident in an otherwise apparently well child.

This condition is not rare, there having been about 60 cases reported in the past 50 years, 18 in the American literature. Nevertheless, it is uncommon enough that, unless recognized as an entity, considerable confusion and unnecessary diagnostic procedures may result.

Historical Review

Batten,[1] in 1907, was probably the first to describe this entity. He presented an 11-year-old boy who, without preceding illness, suddenly developed headache, vomiting, and ataxia. He had nystagmus, some loss of tone in the legs, and active knee jerks. He recovered completely in three weeks. Taylor,[2] in 1913, reported two cases, a 7-year-old and a 10-year-old girl, each having sudden ataxia with recovery in 3 and 10 weeks, respectively. Griffiths[3] reviewed 31 cases of acute cerebellar encephalitis reported in the literature up to 1921 and added two similar cases. In most of the remainder, an acute infectious disease had immediately preceded the ataxia, and there was more widespread involvement of the nervous system.

Klingman and Hodges,[4] in 1944, reported seven cases of acute ataxia of unknown origin in children, six of which seemed to fit the criteria of acute cerebellar ataxia defined in this paper. In four of these patients neutralizing antibodies against St. Louis and eastern equine encephalitis were absent, and in two, whose serum was also tested against western equine encephalitis, louping ill, lymphocytic choriomeningitis, and herpes simplex antibodies were not found. Dekker-Jonker[5] published eight more cases in 1948. Keller and Karelitz[6] added a 20-month-old girl who had dyskinetic eye movements in addition to cerebellar ataxia. The latter improved, but nystagmus and internal strabismus were present 10 months later.

Shanks[7] divided 39 cases of childhood cerebellar ataxia seen between 1929 and 1949 into two groups: 22 with an acute onset and 17 with an insidious onset. While some of the former probably are instances of the entity under discussion, no case histories are given. It was his impression

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that those with a rapid onset and maximal ataxia have a better prognosis than those whose ataxia develops slowly and progressively.

Theiffry, Martin, and Arthuis [8] reported eight cases in 1953. The children were between the ages of 16 months and 3½ years, and all recovered without sequelae within one to eight weeks. They considered the disorder to be a distinct entity of undetermined etiology characterized by the abrupt onset of pure cerebellar symptomatology, sometimes so impressive that the parents recall the exact hour it began.

Five typical cases were added by Berglund, Mossberg, and Rydenstam [9] in 1955. They suggested that the symptoms may have been related to an influenzal infection in three of these cases. The serological evidence to support this consists of paired samples from one patient showing some rise in titer against influenza B; a positive, convalescent, unpaired sample against influenza B in one, and a positive, convalescent, unpaired sample against influenza A in another. The evidence that some of these symptoms may be related to poliomyelitis is somewhat greater. From each of the other two patients Berglund et al. recovered Type I poliomyelitis virus during the acute illness, showed the presence of neutralizing antibodies against Type I poliomyelitis, and demonstrated a positive complement-fixation reaction against poliomyelitis virus.

Rohmer, Isch, and Gangloff [10] reported a characteristic case in 1956. In 1957 Schwarz, King, and Slade [11] discussed nine patients, some of whom had involvement of the cerebrum, brain stem, and/or spinal cord. In a few cases persistent ataxia and residual behavior disorders occurred. From the description of the syndrome, however, most of the cases seem to fall into the group we are presenting. On one child virus studies for lymphocytic choriomeningitis; mumps; lymphogranuloma venereum; Q-fever; "adenovirus"; poliomyelitis virus Types I, II, and III, and herpes simplex were all negative.

A recent review of the literature was made by Cottom [12] in 1957, at which time he estimated that 33 cases had been described. In addition to those we have mentioned, he includes one case reported by Merle and three described by Barbonneix and describes seven of his own. Virus studies were undertaken in three of his cases. In two no virus was isolated, but in the third a cytopathogenic agent was recovered, though the virus had not yet been identified.

Present Study

We are reporting 20 cases of this syndrome seen at the Indiana University Medical Center and the Indianapolis General Hospital from 1948 through 1957. We have eliminated cases of cerebellar ataxia accompanying the exanthemata or other defined infectious diseases as well as those of diffuse encephalitis, in which cerebellar involvement is but an associated aspect of widespread brain dysfunction manifested by stupor, convulsions, hemiplegia, aphasia, ocular palsies, and abnormal involuntary movements.

The Table summarizes the clinical records of our 20 patients.

Comment

Clinical Features.—From these data it is apparent that this disorder is one that occurs predominantly in early childhood. Of the 20 patients all but 3 were between the ages of 9 months and 4 years; the remainder were 7 and 8 years old. Premonitory symptoms of listlessness, drowsiness, fever, vomiting, headache, or a cold were present in 13 and preceded the ataxia by one or several days. However, the main feature was the rapid development of ataxia, which always affected the trunk and legs, and, in one-half, the arms as well. Parents often described the child as "walking like he's drunk." Nystagmus was observed in only two instances, while in one there were peculiar rapid oscillations of the eyes with associated flickering of the lids for a few days. In no instance were abnormalities

Summary of the Clinical Records of Our Twenty Patients

Case	Date	Age, Yr.	Adm. Diagnosis	Temp., F	CSF WBC	CSF Prot.	Blood WBC	Symptoms *	Physical Symptoms	EEG	Follow-Up
1	1/48	5	?Cerebellar lesion, ?polio	98.8 100.4	2	22	6,300	2D weak legs; ataxic uppers; unable to feed self; slurred speech	Ataxic arms, legs, and trunk; nystagmus		Recovered 10 wk.
2	8/48	3	Cerebellar ataxia, tumor	98. 100.6	0	20	4,200	4D listless; DA staggering	Fretful, unsteady gait		Recovered 2 wk.
3	11/48	7	Tumor, hemorrhage, encephalitis	99.2 99.8	25	26	12,000	8D PTA vomiting, drowsy; 6D twitching fingers, headache	Ataxic arms, legs, and trunk; rapid oscillations of eyeballs; flicker of lids	Normal	Recovered 7 wk.
4	1/49	2	?Cerebellar ataxia	98.8 101.	10	26	8,800	14D PTA cold for few days; 7D fever, staggering	Ataxic gait and trunk, hyporeflexia	Normal	Recovered 11 wk.
5	9/49	3	Cerebellar encephalitis	102.	67	..	8,600	3D weak legs; 1D fever; vomiting	Ataxic gait and trunk, hyporeflexia		Recovered 3 wk.
6	10/49	2	Cerebellar encephalitis	103.4	17	18	11,800	1D listless, staggers, ataxic uppers, dizzy	Ataxic trunk, left arm, and leg		Recovered 2 wk.
7	10/50	2	?Tumor	99.2 100.	19 ..	70 bloody; 30 less bloody	7,000	2D fever, sore throat, pain in legs; 1D vomiting, weak, unable to walk, irritable	Fretful; ataxic trunk, legs, and rt. arm	Minimal change rt. post.	Recovered 6 wk.
8	10/50	4	Cerebellar ataxia, ?polio	99. 100.5	160	50	13,000	3D sore throat; 2D pain in left leg, anorexia, vomiting	Ataxic trunk, arms, and gait		Recovered 7 wk.
9 †	7/52	3	?polio	100. 100.6	117	27	11,090	4D staggering, shaking of hands, progressive	Ataxic trunk and legs; hyporeflexia		Persistent mild ataxia 3 mo. later, behavior disorder, petit mal
10	1/53	21 mo.	Tumor, poison, encephalitis	100.	0	17	4,500	3D cold; 1D fever, DA unable to walk	Ataxic trunk and legs		Recovered 4 wk.
11	4/53	8	?Encephalitis, ?emotional problem	101.4 102.5	86	22	9,300	1 mo. headache, listless; 1D headache; DA unable to walk, dizzy	Ataxic trunk and legs	Diffuse superficial cortical dysfunction	Improved 3D; no follow-up
12 †	6/53	8	Cerebellar encephalitis	97.8 100.2	4	10	8,900	DA dizzy on standing	Ataxic trunk and legs, nystagmus		Recovered 4 wk.
13	7/53	2	Ataxia	97.4 100.	0	..	10,750	4D PTA vomited once; became ataxic, drowsy; unable to sit or hold head up	Ataxic trunk and legs		Recovered 4 wk.
14	3/54	2	Cord tumor, transverse myelitis	100. 101.5	0	60	10,300	14D cough, cold; 7D staggering, falling	Irritable, ataxic trunk, hyporeflexia	Normal	Recovered 4 wk.
15	4/55	4	Encephalitis tumor, labyrinthitis	99.6 100.2	750	87	12,300	14D PTA headache for 1D; 7D vomiting with 1D fever; 2D drowsy; 1D falling; ataxia	Lethargic, trunk ataxia; hyporeflexia	Normal	Recovered 6 wk.
16	5/55	4	Encephalitis	98.4 99.2	1	22	12,800	3D stomach ache; 2D vomiting, staggering, lethargy	Ataxic arms, legs, and trunk		Recovered 3 wk.
17	6/55	2	Encephalitis	99.8 102.6	2	55	10,900	DA irritable, unable to stand, trembles all over, frequent vomiting	Ataxic trunk and legs		Improved 5D; no follow-up
18	11/55	2	?Subdural tumor	98.6	0	19	6,600	DA ataxia, vomiting	Ataxic arms, legs, and trunk		Recovered 3 wk.
	3/57	3	?Cerebellar encephalitis	98.6	2	20	5,050	3D staggering, vomiting	Severe ataxia of arms, legs, and trunk	Diffuse slow waves; 4 mo. later normal	Recovered 2 wk.
19	6/56	2	Encephalitis	99.6 100.6	0	10	8,050	14D unable to walk on awakening, gradually improved	Ataxic arms, legs, and trunk	Minimal diffuse abnormality	Improved 4D no follow-up
20	12/56	9 mo.	FUO,* intracranial lesion	103. 103.	3	75	17,800	14D shook head laterally, 3D nystagmus; 2D listless; 1D vomiting	Ataxic arms, legs, and trunk	Minimal change lt. sylvian fissure; normal 4D later	Recovered 2 wk.

* D, day; DA, day of admission; PTA, prior to admission; FUO, fever of undetermined origin.
† Patients 9 and 12 are siblings.

detected in the ocular fundi. The hyporeflexia often seen in cerebellar lesions was common. Neurological examination disclosed no clinical evidence of involvement of structures other than the cerebellum. A number of the children were fretful and irritable early in their illness, but this shortly subsided, so that within a few days they were alert and cheerful.

Improvement usually began after several days and in some instances was remarkably rapid. The average period for complete recovery was five weeks. In three children improvement began within five days, but there was no follow-up examination after release from the hospital. Only one child (Case 9) had residual deficits. She developed petit mal, had a severe behavior problem, and was mildly ataxic three months after discharge.

Ordinarily the children have a single episode of ataxia. However, two had relapses. One (Case 7) had a short period of ataxia three weeks prior to admission, from which he recovered. He relapsed, was hospitalized, and improved in a week. In the following week he had a third episode, from which he recovered in six weeks. Another child (Case 18) had her first attack at the age of 2 years and recovered in three weeks; then she had a second episode, a year later, recovering in two weeks. The onset in this second attack was startling, the child suddenly falling off a davenport in a state of ataxia.

The disease was not accompanied by a notable elevation of temperature. Thirteen children had rectal temperatures of 100 F or less on admission, and the average peak temperature was 101 F, which quickly declined. Two children with higher temperatures had nasopharyngeal pneumococcal infections.

The white blood cell count was below 10,000 per cubic millimeter in 10 cases and slightly elevated in 9. One patient had a count of 17,800.

In 12 instances the cerebrospinal fluid white cell count was below 10; in three it was between 10 and 25; in the remaining five there was pleocytosis, with a count of 67 to 750, predominantly lymphocytes. The total protein of the cerebrospinal fluid was below 50 mg. % in 14 instances, between 55 and 87 mg. % in 4, and not determined because of insufficient quantity of fluid in 2.

An occasional blood sample was obtained from the more recent patients for complement-fixation reactions. Unfortunately, there were no paired specimens. An acute specimen from Case 19 gave a 4+ complement-fixation reaction in a 1:32 dilution against mumps and a negative CF reaction to St. Louis encephalitis, eastern and western equine encephalomyelitis, and lymphocytic choriomeningitis. In all other instances where serum was available negative reactions were obtained. The laboratory received two stool samples each from Cases 16 and 20. Cytopathogenic agents were not recovered from the stools. It is recognized that these laboratory data are completely inadequate.

Electroencephalograms were done on eight patients. They were normal in three; there were minimal abnormalities in five. A second EEG in one of these was normal in four days; another, done four months after the first EEG, was normal. The remaining three patients with abnormal records were not reexamined.

It appears, therefore, that this disease provokes little systemic response to whatever may be the etiologic agent, a fact in keeping with its benign course. Furthermore, there were no correlations between the temperature on admission, the leukocyte response, the cerebrospinal fluid findings, the EEG changes, and the period of recovery.

Differential Diagnosis.—The admission diagnoses depict the variety of conditions requiring differentiation. These consisted of encephalitis, poliomyelitis, labyrinthitis, intracranial hemorrhage, transverse myelitis, subdural hematoma, poisoning, and hysteria.

Posterior fossa tumors ordinarily do not show the rapid development of ataxia and short duration of early symptoms seen in these cases. Headache is more intractable and severe; the child tends to hold his head tilted and to avoid movement; papilledema and abducens nerve palsy develop during the course of illness, and the child's symptoms worsen.

Acute "serous" labyrinthitis is associated with nausea, vomiting, and severe vertigo aggravated by postural changes of the head. Nystagmus is practically always present; tremor, if it occurs, is static rather than intentional; disorders of equilibrium accompany the vertigo.

Encephalitis is manifested by confusion, lethargy, stupor, delirium, and frequently by convulsions, pupillary abnormalities, or focal cortical irritation. Cerebellar dysfunction may be an accompaniment of a diffuse brain inflammation. In the cases under discussion the symptomatology is clinically confined to the cerebellum, and we have eliminated those cases with more extensive nervous system dysfunction.

Drug intoxication frequently produces ataxia, and, if one is unaware of the history of ingestion of drugs, the cause of the child's ataxia may very easily be missed. However, if the child is sufficiently toxic there will be delirium, disorientation, stupor, and perhaps hallucinations. Recovery generally occurs in a few days rather than weeks.

Differentiation from hysteria can be very difficult. However, in hysteria the ataxia is more bizarre, the stance is more grotesque, and there are associated emotional and behavioral aspects. Furthermore, the premonitory symptoms of systemic illness, often present in the ataxic child, are absent.

Poliomyelitis, myelitis, subdural hematoma, and intracranial hemorrhage are not accompanied by distinct cerebellar symptoms. Acute multiple sclerosis is rare in children under 10 years of age, and the symptomatology is not confined to the cerebellar system.

Etiology.—We are unable to assign any specific etiology to this syndrome. Although a viral agent has been suspected by many authors, conclusive evidence for this is not yet forthcoming. Our own series does not shed enough light on the etiology to warrant an opinion, although from the clinical characteristics we presume a viral infection.

Summary and Conclusions

Twenty cases of acute cerebellar ataxia in children, unassociated with any definite etiology, are presented. The condition is an entity characterized by the abrupt onset, with or without prodromata, of ataxia affecting mainly the trunk and legs and in some instances the arms; by minimal systemic reactions; by inconstant changes in the cerebrospinal fluid, and by practically invariable recovery within days or weeks. Children under 4 years of age are most frequently affected. Residua rarely occur. Occasionally a child will have more than one episode of ataxia. The etiology is undetermined but is presumably a viral infection.

The most important conditions in differential diagnosis are posterior fossa tumor, acute labyrinthitis, encephalitis, drug intoxication, and hysteria. The differential features of each are discussed.

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REFERENCES

1. Batten, F. E.: Case of Acute Ataxia, Tr. Clin. Soc. London 40:276, 1907.

2. Taylor, E. S.: Notes on 4 Cases of Cerebellar Ataxia in Children, Guy's Hosp. Rep. 67:98, 1913.

3. Griffiths, J. P. C.: Acute Cerebellar Encephalitis (Acute Cerebellar Ataxia), Am. J. M. Sc. 162:781 (Dec.) 1921.

4. Klingman, W. O., and Hodges, R. G.: Acute Ataxia of Unknown Origin in Children, J. Pediat. 24:536 (May) 1944.

5. Dekker-Jonker, A.: Acute cerebrale tremor en ataxie bij jonge kinderen, Nederl. tijdschr. geneesk. 92:2912 (Sept. 18) 1948.

6. Keller, M. J., and Karelitz, S.: Acute Ataxia in a 20-Month-Old Female, Pediatrics 1:754 (June) 1948.

7. Shanks, R. A.: Notes on Cerebellar Ataxia in Childhood, Arch. Dis. Childhood 25:389 (Dec.) 1950.

8. Thieffry, S.; Martin, C., and Arthuis, M.: L'Ataxie cérébelleuse aiguë curable de l'enfant, Arch. franç. pediat. 10:14, 1953.

9. Berglund, G.; Mossberg, H-O., and Rydenstam, B.: Acute Cerebellar Ataxia in Children, Acta paediat. 44:254 (May) 1955.

10. Rohmer, A.; Isch, F., and Gangloff, D.: Ataxie cérébelleuse aiguë curable, Arch. franç. pediat. 13:426, 1956.

11. Schwarz, G. A.; King, G. A., and Slade, H.: Acute Idiopathic Cerebellar Disorders of Childhood, A. M. A. Arch. Neurol. & Psychiat. 78:479 (Nov.) 1957.

12. Cottom, D. G.: Acute Cerebellar Ataxia, Arch. Dis. Childhood 32:181 (June) 1957.

Complications Following the Use of Prochlorperazine (Compazine) as an Antiemetic

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Introduction

Vomiting, as a manifestation either of acute infection or of other illness, is a very common problem in pediatric practice, and a variety of agents have been used in an attempt to control this symptom. In the past few years certain phenothiazine derivatives have been demonstrated to exert very definite antiemetic effects. Chlorpromazine has been evaluated by clinical trial in several studies in both adults [1-3] and children [4,5] and has been found to be a very effective antiemetic but to be accompanied in an occasional case by undesirable side-reactions. These have included somnolence, Parkinsonism, hypotension, agranulocytosis, and jaundice. More recently, prochlorperazine, a related phenothiazine derivative, has been similarly shown to be very effective as an antiemetic [6] and has been widely used for the control of vomiting in infants and children. It was hoped that the unpleasant side-effects might be less common. In general, it would appear that this expectation has been borne out, but we have encountered bizarre symptoms in four patients which appear to be related to the administration of prochlorperazine. These patients are described in the following case histories.

Report of Cases

CASE 1.—*History.*—On Jan. 31, 1957, an 8-year-old white girl was admitted to the Jackson Memorial Hospital because of spasms and tenderness of the sternomastoid and masseter muscles. Two days prior to admission she developed a temperature of 102 F, diarrhea, and vomiting. During the day before coming to the hospital she was given a total of 15 mg. of oral prochlorperazine* for her vomiting. Approximately 12 to 15 hours after receiving the prochlorperazine she developed spasm and tenderness in the aforementioned muscle groups.

Physical Examination.—Spasm and tenderness of the right sternomastoid muscle caused her to rotate her head to the right. There was intermittent bilateral spasm of the masseter muscles; with encouragement, however, the child was able to relax these muscles and to open her mouth, but the trismus would recur when her attention was not directed toward control of these muscles. There was no tightness or spasm of the abdominal muscles. The neurological examination was otherwise negative.

Laboratory Data.—Hemoglobin, 12.4 gm/100 ml.; white cell count, 8150 per cubic millimeter, with a differential count of 40% segmented forms, 31% band forms, 25% lymphocytes, and 4% monocytes. Serum chemical studies showed CO_2, 21.1 mEq. per liter; chlorides, 109.4 mEq. per liter; sodium, 140 mEq. per liter; potassium, 4.7 mEq. per liter; calcium, 10.4 mg. %. Stool culture showed no enteric pathogens. ECG was within normal limits.

Hospital Course.—The girl's spasms lasted for approximately 12 hours and subsided without specific therapy. She was observed in the hospital for an additional two days, without recurrence of her symptoms. The child has subsequently remained normal. It was thought that this child's primary illness was acute gastroenteritis, which was complicated by the administration of prochlorperazine.

CASE 2.—*History.*—On Jan. 22, 1958, a 7-year-old Negro boy was admitted to the Jackson Memorial Hospital because of spasm of the neck muscles causing the head and neck to deviate to the right side. Two days previously he had been seen at another hospital with a complaint of cough, rhinorrhea, and vomiting without fever. He was treated with procaine penicillin and streptomycin

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* In all four of these children Compazine was the brand of prochlorperazine administered.

intramuscularly, a standard cough medication, and prochlorperazine, 10 mg. sustained release capsules (Spansules). He was given 1 capsule of prochlorperazine every 12 hours for vomiting. Three hours after he was given his second dose he began to complain of temporal headaches, vomiting recurred, and he was noted to have paroxysmal drawing of his head towards the right shoulder. During the attacks he was reported to drool excessively. He responded to questioning but seemed to be unable to hold his head in an erect position. During the next 24 hours the aforementioned symptoms continued with increased frequency, lasting from 2 to 5 minutes. Between these episodes he was able to hold his head in a "normal" position. His sensorium was normal, and he could remember each attack, but he stated that he had no control over his actions during these episodes. His mother noted that these attacks started from three to five hours after the administration of each prochlorperazine capsule, and so after the fourth capsule was given she stopped the medication and brought him to our hospital for treatment. He gave no past history of convulsions and was doing well in school. He was considered to be a bright courteous boy with no emotional difficulties. There was no family history of convulsive disorders.

Physical Examination.—On physical examination he was noted to hold his head flexed toward his right shoulder. There was spasm and tenderness of the right sternomastoid muscle. With assistance, the head could be returned to an upright position. There appeared to be some spasm of the right masseter muscle causing some distortion of the right side of the face. He drooled excessively and spoke with some difficulty. The deep tendon reflexes were hyperactive, and the remainder of the physical and neurological examination was negative.

Laboratory Data.—Hemoglobin, 11.9 gm/100 ml.; white cell count, 6700 per cubic millimeter, with a differential count of 58% segmented forms, 5% band forms, 36% lymphocytes, and 1% monocytes. Urinalysis was normal. Results of lumbar punctures were as follows: Jan. 22, 1958—crystal-clear fluid, pressure not taken; cells, 1 per cubic millimeter; sugar and protein were normal. Culture was sterile. Jan. 27, 1958—crystal-clear fluid, initial pressure 90 mm. of H_2O; cells, 5 monocytes and 25 RBC per cubic millimeter; sugar and protein were normal. Culture was sterile. X-rays of the skull were normal. Virus studies on blood serum and stool were normal.

Hospital Course.—Shortly after admission to the hospital the patient's spasms subsided without treatment. He remained afebrile and had no complaints. He had no return of his vomiting. The nurses considered him to be a well-mannered and well-adjusted boy. An EEG which was done approximately 60 hours after admission showed diffuse disorganized brain activity with some asymmetry over the right hemisphere. Five days later the EEG was repeated and showed a moderate improvement. At this time, he was again given prochlorperazine capsules, 10 mg. every 12 hours, in an attempt to reproduce his symptoms. After he received his sixth prochlorperazine capsule he began to complain that his tongue was being "drawn up" and that he had a headache. Following this he vomited and complained that his "eyes hurt." About this time his actions became violent. He began to hit, kick, and bite the nurses. He was noted again to hold his head flexed and had excessive drooling. At this point administration of prochlorperazine was discontinued. After 12 hours he again was calm and courteous. He had some recollection of his previous behavior but stated that he was unable to control his actions at that time. A third EEG was taken at this time, which showed improvement over the previous two. After the drug was discontinued he had no repetition of these "attacks," and the remainder of his hospital course was uneventful. The primary diagnosis in this child was believed to be an acute respiratory infection with gastroenteritis.

CASE 3.—*History.*—On Jan. 29, 1958, a 6-month-old Negro girl was admitted to the Jackson Memorial Hospital with the diagnosis of possible meningitis. She was seen in the emergency room with opisthotonos and having tonic convulsive spasms. The head and eyes were turned to the right side. Two days previously she had been seen in the emergency room with fever (temperature, 102.4 F), cough, vomiting, and diarrhea. She was given an injection of benzathine penicillin G, triple sulfonamides by mouth, and phenylephrine (Neo-Synephrine) nose drops. The following evening (12 hours prior to admission) she was taken to her family physician because of persistence of the vomiting and diarrhea. She was given an injection of procaine penicillin and 2.5 mg. of prochlorperazine intramuscularly. Shortly after returning home she was given an additional 2.5 mg. of prochlorperazine by mouth. Four hours after this she developed spasms of the extremities, her head was thrown back, and the eyes turned to the right. These paroxysmal attacks continued during the next eight hours, when she was again returned to the emergency room in this hospital. She was admitted to the hospital with a tentative diagnosis of meningitis.

Physical Examination.—Temperature was 100.6 F. The infant was in an opisthotonic position and had tonic flexion of all extremities. The head and eyes were rotated to the right side. The fontanel was flat; the deep tendon reflexes were hyperactive. The remainder of the examination was

normal, except for slight injection of the mucous membranes of the nose and throat.

Laboratory Data.—Hemoglobin, 9.9 gm/100 ml.; white cell count, 9500 per cubic millimeter, with a differential count of 43% segmented forms, 6% band forms, 49% lymphocytes, and 2% monocytes. Serum chemical studies showed CO_2, 20.1 mEq. per liter; chloride, 100.9 mEq. per liter; sodium, 139 mEq. per liter; potassium, 4.25 mEq. per liter; sugar, 109 mg. %. Lumbar puncture yielded crystal-clear fluid, initial pressure not taken; cells, 3 monocytes and 5 RBC per cubic millimeter; sugar, 68 mg. %; protein, 11 mg. %. Spinal fluid culture showed no growth after 48 hours.

Hospital Course.—Because of the history of having received prochlorperazine and the normal laboratory findings the infant was given only sedation. During the following 12 hours the spasm had subsided and the infant was considered to be improved; however, she was still considered to have some rigidity of the extremities. After 24 hours she was considered normal and was observed for the next 3 days but had no return to her previous symptoms. The original illness was thought to be an acute gastroenteritis and a respiratory infection.

CASE 4.—*History.*—On Dec. 27, 1957, a 6-year-old white girl was admitted to Variety Children's Hospital because of inability to open her mouth and to speak normally. In addition, she also had vomiting and moderate dehydration. Eight days prior to admission she had developed nausea with episodes of vomiting. During the next seven days the aforementioned symptoms continued. On the day before admission, because of the continuing vomiting, she was given prochlorperazine, 5 mg. four times a day, by the family physician. At this time, she was also noted to have tonsillitis, and so oxytetracycline therapy was started. After receiving her third prochlorperazine capsule she became sleepy and lethargic. At this point, the physician advised that the prochlorperazine be discontinued. Shortly after this, however, she began to complain of difficulty in swallowing and an inability to move her tongue. Her parents noted that she had difficulty opening her mouth, and that she was drooling. They noted also that her speech was not normal. Her family physician advised hospitalization at this time. The child's past history was noncontributory, and there was no family history of convulsions or of unusual neurological or psychiatric disorders.

Physical Examination.—On examination the patient was afebrile and appeared slightly lethargic. She held her mouth in a closed position but was able to open it with encouragement and assistance. Her speech was considered to be slurred. The deep tendon reflexes were hyperactive, and there was a positive Babinski sign on the left side. There was no spasm or tenderness of the muscles of the abdomen or extremities. The mucous membranes of the nose and throat were slightly injected, but no purulent exudate was present. The remainder of the physical and neurological examinations were considered to be normal.

Laboratory Data.—Hemoglobin, 10.8 gm/100 ml.; white cell count 5900 per cubic millimeter, with a differential count of 69% segmented forms, 2% band forms, 27% lymphocytes, and 1% eosinophils. Urinalysis was normal. Throat culture showed no pathogenic organisms. X-ray of chest was normal.

Hospital Course.—Because the patient was considered to have a toxic reaction to prochlorperazine, she was observed and given fluids intravenously for her moderate dehydration. After 12 hours in the hospital the inability to open her mouth and to speak normally had disappeared. She was now able to take liquids by mouth and was considered to be normal. She was observed an additional three days in the hospital, without recurrence of her symptoms. It was thought that the original illness, which was complicated by therapy, was acute gastroenteritis associated with a respiratory infection.

Comment

Although perhaps not widely recognized, these peculiar reactions, as manifested by spasm of various muscle groups, particularly of the neck and face with trismus and opisthotonos, have been previously described as occurring following the administration of both chlorpromazine [7,8] and prochlorperazine.[6] DeGennes and Bricaire [9] have also reported three patients with symptoms very similar to those reported here following the use of another analogue of prochlorperazine, 3-chloro-10-[3-(1-methyl-4-piperazinyl)propyl]-phenothiazine. In reported cases, as in those described here, there has been rather prompt subsidence of symptoms following withdrawal of the drug, with no apparent residua. These symptoms have been ascribed to involvement of the extrapyramidal nervous system and have been associated in previous reports [6] with large doses of the drug. Scrutiny of the above cases as regards the relationships of toxic manifestations to dosage of the drug reveals that three (Cases 1, 2, and 4) received prochlorperazine orally in dosage not exceeding that recom-

mended by the manufacturer, while one patient (Case 3) received amounts which might be considered somewhat in excess of the recommended dose. It would appear likely, therefore, that reactions represent an individual sensitivity to the drug rather than a manifestation of overdosage. It seems highly unlikely that the reactions described in these patients could have been a manifestation of the primary illness, which was acute gastroenteritis associated in most cases with acute respiratory infection. This is particularly indicated by the fact that the symptoms were reproduced in Case 2 by administering the drug a second time. That acute infection might play a part in predisposing the child to react to such drugs may be worthy of consideration, however.

The electroencephalographic findings reported in Case 2 have no apparent correlation with reaction to the drug. Although the initial record was considered abnormal, there was steady improvement in subsequent records, including one taken on the day when symptoms had been reproduced by prochlorperazine administration.

It appears that the reactions described here are not of serious consequence as regards long-lasting effects but do present the physician with a difficult diagnostic problem unless he is aware of such manifestations. Two cases were considered, when first seen, to have meningitis, while in two cases a diagnosis of tetanus was entertained, owing to the marked spasm of masseter muscles. It is, therefore, considered desirable to acquaint pediatricians with this type of reaction to prochlorperazine. Although the exact incidence of such reaction is unknown, it is probably low, since there is a widespread use of the drug, with a very small number of reactions having been noted.

Summary

Four cases are reported which appear to represent side-effects of prochlorperazine administration as manifested by spasm of voluntary muscles, particularly of the neck, face, tongue, and spine. Although without significant sequelae, such reactions may constitute a problem in diagnosis, necessitating diagnostic studies, which can perhaps be avoided if physicians are made aware of the nature of such reactions.

Jackson Memorial Hospital (36).

REFERENCES

1. Friend, D. G., and Cummins, J. F.: New Antiemetic Drug: Preliminary Report, J. A. M. A. 153:480-481 (Oct. 3) 1953.
2. Knight, R. W.; Kent, B.; Morris, G., and Rogers, S.: Clinical Studies of an Antiemetic Agent, Chlorpromazine, J. Lab. & Clin. Med. 42: 828 (Nov.) 1953.
3. Connor, P. K., and Moyer, J. H.: A Therapeutic Appraisal of Antiemetic Agents, GP 14: 124-139 (Nov.) 1956.
4. Steigman, A. J., and Vallbona, C.: Chlorpromazine, a Useful Antiemetic in Pediatric Practice, J. Pediat. 46:296-297 (March) 1955.
5. Daeschner, C. W.; Colgan, M.; Brewer, E.; Foster, J., and Bashaw, C.: Evaluation of Antiemetic Agents in Control of Vomiting in Children, South. M. J. 49:1465-1469 (Dec.) 1956.
6. Connor, P. K., and Moyer, J. H.: Preliminary Clinical Observations on a Potential Antiemetic Agent, Prochlorperazine (Compazine), Antibiotic Med. 4: 508-514 (Sept.) 1957.
7. Cohen, I. M.: Complications of Chlorpromazine Therapy, Am. J. Psychiat. 113:115-121 (Aug.) 1956.
8. Hollister, L. E.: Complications from the Use of Tranquilizing Drugs, New England J. Med. 257:170-177 (July 25) 1957.
9. DeGennes, L., and Bricaire, H.: Les Accidents nerveux d'un nouvel antiémétique (6140 RP), Presse méd. 65:499 (March 16) 1957.

Oral Phenoxymethyl Penicillin Therapy in Prophylaxis of Recurrent Rheumatic Fever

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Prior to the advent of chemotherapeutic and antibiotic agents, streptococcal disease and its complications accounted for about 10% of deaths in the pediatric age group. Although this figure has been reduced to less than 1%, the most serious complication at present is that of acute rheumatic fever. It has been shown that this complication can be prevented by adequate treatment of the preceding streptococcal infection.[1,2] Bland and Jones [3] have demonstrated that recurrences of rheumatic fever or chorea are common and occur in approximately 20% of patients during the first five years after the initial episode of acute rheumatic fever. Although the mortality rate in the first episode of acute rheumatic fever is low, residual cardiac damage results in an appreciable mortality and morbidity in later years.[3-5] The severity of the cardiac damage is increased with each recurrence of acute rheumatic fever, and so prevention of recurrences is imperative. During the period 1943-1956, children who attended our cardiac clinics were given sulfonamides orally as a prophylactic measure against recurrences.[6,7] During the last two years oral administration of phenoxymethyl penicillin (penicillin V) has been used exclusively in these patients as the prophylactic measure. This is a report of the results in a group of 266 patients.

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The phenoxymethyl penicillin used in this study was supplied by Eli Lilly & Company in the form of V-Cillin.

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From the Children's Hospital Research Foundation, Department of Pediatrics, College of Medicine, and the Cincinnati Children's Heart Association.

Method

All patients admitted to the study had had at least one previous episode of acute rheumatic fever, the diagnosis of which depended on the modified Jones criteria.[8] The patients were seen in the cardiac clinics every two to three months. During these visits particular attention was paid to eliciting any intercurrent history suggestive of rheumatic fever. This included a history of joint pains or swelling, sore throat, fever, epistaxis, skin rashes, subcutaneous nodules, or failure to gain weight. Any change in physical signs which might have been due to a reactivation of the rheumatic infection or progression of the cardiac disease was noted. Fluoroscopic examination of the chest was undertaken at least every six months to determine any change in cardiac size or configuration. Electrocardiograms, including use of standard and unipolar extremity and chest leads, were recorded at least every six months. Particular attention was paid to the cardiac rhythm, duration of electrical systole, and evidence of ventricular hypertrophy.

During each clinic visit a nasopharyngeal culture was obtained by passing a sterile wire swab through a nostril back along the floor of the nasal passage until contact was made with the posterior nasopharyngeal wall. The swab was left in this position for a few seconds and withdrawn. The specimen was placed in a large Pyrex glass tube which contained a smaller test tube with 4 ml. of blood broth (trypticase soy broth BBL to which 2% fresh defibrinated rabbit blood had been added) and penicillinase, into which the cotton tip was completely immersed. The inoculating procedures carried out very soon after obtaining the specimens were as follows.

(*a*) The cotton tip of the wire swab was spread over one-third of the area of each of four blood agar plates (trypticase soy agar BBL with 5% fresh defibrinated rabbit blood). Care was taken to rotate the swab as it was wiped back and forth on the blood agar plates in order to assure thorough sampling. The plates were then streaked with

a sterile wire loop. Two blood agar plates were incubated in air at 37 C for 18 to 24 hours, and the other two were placed in a candle jar for incubation at 37 C for 18 to 24 hours in an atmosphere of increased carbon dioxide tension.[38]

(*b*) Then 0.2 ml. of crystal violet 1:25,000 and 0.3 ml. of sodium azide 1:1000 were added to the 4 ml. of blood broth which contained the nasopharyngeal swab. After adequate mixing by drawing the material back and forth from a pipette, the tubes were incubated at 37 C for 18 to 24 hours. The tubes were then subcultured on two blood agar plates which were incubated in a candle jar at 37 C for 18 to 24 hours. Sodium azide and crystal violet were added to the blood broth (according to the method of Pike) to inhibit the overgrowth of Gram-negative and Gram-positive organisms other than streptococci.[9,10] The value of this medium has been confirmed by Feldman and Harmon,[11] the Commission on Acute Respiratory Diseases,[12,13] and Kuroda and Feldman.[14]

After incubation the blood agar plates were examined. Two or more of each different type of colony which might possibly be β-hemolytic streptococci were picked from each plate and subcultured on a blood agar plate and in a tube containing 2.0 ml. of blood broth. After incubation Gram stains were made from the blood broth and examined microscopically. Organisms with colonial and morphologic characteristics of β-hemolytic streptococci were then inoculated in semi-solid blood agar in screw cap tubes and stored at 4 C. At the same time, a blood agar slant was inoculated and after incubation was sent to the Ohio State Department of Public Health Laboratories for serological typing.

Antistreptolysin O titers and C-reactive protein determinations were performed on the serum of venous blood collected at six-month intervals. The antistreptolysin O titers were determined according to the method of Rantz and Randall,[15] as suggested by Difco Laboratories, Detroit. In the C-reactive protein determinations, the serum of Schieffelin and Co., New York, was used.

Each patient received 125 mg. (200,000 units) of phenoxymethyl penicillin orally daily throughout the period of study. They were instructed to take the phenoxymethyl penicillin in the morning before breakfast. The parents of the patients were instructed to report episodes of intercurrent acute respiratory infections and episodes of fever of undetermined cause. They were also familiarized with the symptoms of acute rheumatic fever and instructed to report any of these manifestations. In the event of an intercurrent acute streptococcal infection, the oral dose of phenoxymethyl penicillin was increased to 625 mg. (1,000,000 units) in divided doses daily for a period of 10 days. Nasopharyngeal cultures were obtained at the onset of the acute episode and treated as described above. Acute and convalescent sera were drawn for determination of the antistreptolysin O titer and the C-reactive protein. When dental extractions were advised, the patient received phenoxymethyl penicillin orally, 625 mg. (1,000,000 units) daily in divided doses on the day before, the day of, and the day after surgery. In the asymptomatic patient with a positive nasopharyngeal culture for β-hemolytic streptococci, the dose of phenoxymethyl penicillin was increased to 625 mg. daily for a period of 10 days.

Results

The results of this study will be divided into two periods, each corresponding to one year of observation.

First Year.—During this period 254 patients who fulfilled the criteria described above were studied. There were no instances of toxic effects from phenoxymethyl penicillin. Although many patients reported with intercurrent infections, in the majority of instances the clinical findings were against the diagnosis of acute streptococcal pharyngitis. This clinical impression was confirmed by the negative nasopharyngeal cultures obtained at the time of infection. In 20 patients the clinical picture at the time of acute infection suggested a complicating streptococcal infection. A nasopharyngeal culture was obtained in these patients, and the dose of phenoxymethyl penicillin was increased to 625 mg. daily. However, in 15 of these patients the nasopharyngeal culture was negative for streptococci. The remaining five patients (i. e., 2% of the total series) had nasopharyngeal cultures positive for β-hemolytic streptococci and a high antistreptolysin O titer which decreased during convalescence. The increased dose of 625 mg. of phenoxymethyl penicillin was maintained for a period of 10 days in these patients, and none developed acute rheumatic fever.

Recurrences: Five patients (2% of the total series) had a recurrence of acute rheumatic fever. One of these patients had complicating subacute bacterial endocarditis (viridans Streptococcus) during the recur-

rence of acute rheumatic fever. A brief clinical summary of these patients follow.

CASE 1.—A 6-year-old white boy had a Pott's procedure for tetralogy of Fallot at the age of 14 months. He developed superimposed rheumatic heart disease at the age of 4½ years, but this was not recognized for a period of six months. When the diagnosis was established, he was treated with large doses of cortisone and a daily oral dose of phenoxymethyl penicillin (125 mg.). A recurrence of acute rheumatic fever with pericarditis and myocarditis occurred nine months after the initial episode and while the patient was still taking cortisone and phenoxymethyl penicillin therapy.

CASE 2.—A 13-year-old Negro boy had the initial episode of acute rheumatic fever in 1952. Three recurrences of acute rheumatic fever were observed between 1952 and 1955 while he was taking sulfadiazine (1.0 gm. daily) prophylaxis. Subacute bacterial endocarditis (viridans Streptococcus) was diagnosed in 1955. A fourth recurrence of acute rheumatic fever occurred while he was taking oral phenoxymethyl penicillin prophylaxis.

CASE 3.—A 14-year-old white boy had acute rheumatic fever with carditis in 1952 and again in 1953 while taking sulfadiazine prophylaxis. Subacute bacterial endocarditis (viridans Streptococcus) and simultaneous acute rheumatic fever occurred during phenoxymethyl penicillin prophylaxis. The subacute bacterial endocarditis was treated for 14 days with phenoxymethyl penicillin, 750 mg. orally every four hours and streptomycin and dihydrostreptomycin 1.0 gm. intramuscularly daily. There was good response to this therapy.

CASE 4.—A 13-year-old Negro boy had three episodes of acute rheumatic fever between 1950 and 1955. He also suffered two separate attacks of subacute bacterial endocarditis (viridans Streptococcus) during this time. A recurrence of acute rheumatic fever occurred while he was receiving phenoxymethyl penicillin prophylaxis.

CASE 5.—An 11-year-old white boy had his initial episode of acute rheumatic fever in 1955. He suffered a recurrence while receiving phenoxymethyl penicillin prophylaxis.

Nasopharyngeal Cultures: Nine hundred forty-three nasopharyngeal cultures were obtained during the first year of study. Nine hundred four (95.9%) were negative for β-hemolytic streptococci. Twenty-six patients (10.2% of the series) had 39 cultures positive for β-hemolytic streptococci. These positive cultures constituted 4.1% of the total series of cultures taken. In 23 of these 26 patients only one positive culture was found, and in these patients the culture became negative after a 10-day period of oral therapy with 625 mg. of phenoxymethyl penicillin. In three patients (1.2% of the total series) more than one positive culture was obtained. None of these patients developed acute rheumatic fever.

Serological Studies: The antistreptolysin O titer * was measured in 202 sera. The titer was less than 166 units in 157 instances. The titer was between 166 and 250 units in 39 sera and greater than 250 units in 6 sera. Although acute streptococcal infections were usually associated with a titer greater than 166 units, there were many instances of a similar titer in asymptomatic patients who had nasopharyngeal cultures negative for β-hemolytic streptococci.

The C-reactive protein was determined in 113 sera. Eight (7.1%) were positive. There was no correlation between the degree of positivity of the C-reactive protein and the symptomatology.

Second Year.—In addition to the 254 patients described above, 12 further patients were admitted to this period of study (total 266). Again there were no instances of toxic effects resulting from use of phenoxymethyl penicillin. Intercurrent acute streptococcal pharyngitis occurred in two patients. These patients were treated with 625 mg. of phenoxymethyl penicillin orally for 10 days, but one patient developed acute rheumatic fever.

Recurrences: One patient (0.4% of the total series) developed a recurrence of acute rheumatic fever. This patient, a 14-year-old white girl, had her initial attack of acute rheumatic fever in 1955. She developed a recurrence of acute rheumatic fever in 1957 while receiving oral phenoxymethyl penicillin prophylaxis. The latter episode was complicated by myocarditis and mitral and aortic valvulitis. It was associated with an elevation of the antistreptolysin O titer to 625 and a negative

* The antistreptolysin O titer is reported in Todd units per milliliter of serum.

C-reactive protein. There was a good clinical response to therapy with prednisone (Meticorten).

Nasopharyngeal Cultures: One thousand seventy-one cultures were obtained during the second year of study. There were 36 cultures which were positive for β-hemolytic streptococci (3.4%). These positive cultures occurred in 30 patients (11.3%), of which 25 (9.4% of the total series) had only one positive culture and 5 (1.9% of the total series) had more than one positive culture. The patients with positive cultures were treated in the same way as described under "First Year."

Serological Studies: The antistreptolysin O titer was measured in 237 sera. The titer was between 166 and 250 units in 21 instances and was greater than 250 units in 49 sera. Again, there was no direct correlation between the height of the antistreptolysin O titer and the clinical state of the patient. In many instances the titer was above 250 units in an asymptomatic patient whose nasopharyngeal culture was negative for β-hemolytic streptococci. However, intercurrent streptococcal infections were usually associated with a rise of the antistreptolysin O titer and a fall during convalescence.

The C-reactive protein was determined in 240 sera. It was positive in 27 instances, with the following distribution: 1+ in 16 instances, 2+ in 2, 3+ in 5, and 4+ in 4. There was no direct correlation between the positivity of the C-reactive protein and the clinical state of the patient.

Serologic Typing of Streptococci.—As indicated above, a total of 2014 nasopharyngeal cultures were obtained (943 in the first year and 1071 in the second year). Seventy-five were positive for β-hemolytic streptococci (39 in the first year and 36 in the second year). Serologic grouping and typing of the 75 positive cultures indicated the following distribution: Group A, 48%; Group C, 10%; Group D, 2%; Group F, 10%; Group G, 12%; not typable, 18%. Although 36 sera were used in attempting to determine the types in Group A, the majority were not typable. The following distribution was found in the Group A β-hemolytic streptococci: Type 12, 10%; Type 13, 5%; Type 25, 5%; Type 33, 10%; not typable, 70%. At the time that a positive culture for β-hemolytic streptococci was obtained it was not appreciated that less than 50% would fall into Group A.

Comment

This study was undertaken when reports became available concerning the efficacy of penicillin in the prophylaxis of acute rheumatic fever.[1,17-19] We were attracted to using phenoxymethyl penicillin orally when it was appreciated that a high blood level of penicillin could be obtained after a single dose of 125 mg.[20] The purpose of the prophylactic medication was to attempt to obtain a sustained tissue level of penicillin.

The regularity of attendance of all patients at an outpatient cardiac clinic is difficult to control because the vast majority are asymptomatic and clinically well. An irregular attendance may occur even after long discussions and explanations to patients and their parents concerning the importance of prophylaxis against recurrences of rheumatic fever. This report includes all patients who were admitted to the study, regardless of the clinic attendance or failure to follow the instructions described above under "Method." Although monthly injections of long-acting repository penicillin were tried in another smaller group of patients, we found that regular clinic attendance dropped off because the parents and the patients refused a monthly painful injection when the patient was feeling well. The disadvantage of oral therapy is that it places the responsibility of maintaining the prophylactic treatment on the patient. However, with oral therapy, the clinic attendance remained at a high level. We have no guarantee that patients receiving oral prophylactic therapy will take the medication regularly or get a higher dose during intercurrent streptococcal infections.

However, it is our belief that it is easier to gain the cooperation of the patients with an oral prophylactic regimen as compared with monthly intramuscular injections. This is especially applicable when it is appreciated that the current recommendations are for a lifetime of prophylaxis once one episode of rheumatic fever has been experienced.

As indicated above, there was a recurrence rate of acute rheumatic fever in 2% of the patients during the first year of study and 0.4% in the second year of study (total of six patients). Three of these six patients had at least three episodes of acute rheumatic fever prior to the institution of penicillin prophylaxis. A fourth patient had a recurrence of acute rheumatic fever while still taking steroid therapy. The natural course of a specific episode of acute rheumatic fever cannot be predicted, and its progression into a subacute phase cannot be ascertained. It is possible that the above four patients were still in an active subclinical phase of rheumatic fever when a clinical recurrence became manifest. However, it cannot be denied that these patients may represent failures of penicillin prophylaxis either due to neglect in taking the phenoxymethyl penicillin or due to the inadequate protection provided by the medication in these specific instances. One episode of viridans Streptococcus subacute bacterial endocarditis occurred during the period of penicillin prophylaxis. Of interest is the fact that this infection was cured by larger oral doses of phenoxymethyl penicillin.

A comparison of the number of recurrences of acute rheumatic fever in the two separate years of study shows an incidence of 2% and 0.4%. This decrease may suggest that the program functioned more efficiently during the second year of study, but it probably restresses the marked variation of the incidence of acute rheumatic fever from year to year. On the other hand, this decrease may be fortuitous. It is probable that the number of recurrences was decreased because asymptomatic patients with β-hemolytic streptococci in the nasopharynx were treated as if they had an acute streptococcal infection.

The marked variation of the antistreptolysin O titer was of interest. In general, the titer rose during convalescence from an intercurrent streptococcal infection. However, the number of high titers obtained in asymptomatic patients was noteworthy. These could be explained by the serum being obtained during convalescence from an unreported acute streptococcal infection.

Summary and Conclusion

More than 250 patients who had experienced at least one episode of acute rheumatic fever were treated with one oral dose of phenoxymethyl penicillin (penicillin V) (125 mg., or 200,000 units) as a prophylaxis against recurrences of acute rheumatic fever.

There were no instances of toxic effects due to oral administration of phenoxymethyl penicillin.

The low incidence of recurrences of rheumatic fever and intercurrent infection due to Group A β-hemolytic streptococci indicates that this form of prophylaxis is practical and successful.

The following physicians managed the patients clinically: Drs. R. A. Lyon, Louise Rauh, E. C. Matthews, F. K. Edwards, C. Weihl, and L. Schwab. The bacteriologic studies were supervised by Dr. M. L. Cooper.

Children's Hospital (29).

REFERENCES

1. Massell, B. F.; Dow, J. W., and Jones, T. D.: Orally Administered Penicillin in Patients with Rheumatic Fever, J. A. M. A. 138:1030-1036, 1948.

2. Denny, F. W.; Wannamaker, L. W.; Brink, W. R.; Rammelkamp, C. H., Jr., and Custer, E. A.: Prevention of Rheumatic Fever: Treatment of the Preceding Streptococcic Infections, J. A. M. A. 143:151-153, 1950.

3. Bland, E. F., and Jones, T. D.: Rheumatic Fever and Rheumatic Heart Disease: A 20 Year Report of 1000 Patients Followed Since Childhood, Circulation 4:836-843, 1951.

4. Wilson, M. G., and Lim, W. H.: The Natural History of Rheumatic Heart Disease in the Third, Fourth and Fifth Decades of Life: I. Prognosis with Special Reference to Survivorship, Circulation 16:700-712, 1957.

5. Magida, M. G., and Streitfeld, F. H.: The Natural History of Rheumatic Heart Disease in the 3rd, 4th, and 5th Decades of Life: II. Prognosis with Special Reference to Morbidity, Circulation 16:713-722, 1957.

6. Lyon, R. A.; Rauh, L. W., and Wolf, R. E.: The Prevention of Rheumatic Fever in Children by the Use of Sulfonamides, Ohio M. J. 43:394-398, 1947.

7. Lyon, R. A.: Prevention of Rheumatic Fever, Kentucky M. J. 47:180-185, 1949.

8. Committee on Standards and Criteria for Programs of Care, American Heart Association: Jones Criteria (Modified) for Guidance in the Diagnosis of Rheumatic Fever, Mod. Concepts Cardiovas. Dis. 24:291-293, 1955.

9. Pike, R. M.: An Environment Broth for Isolating Hemolytic Streptococci from Throat Swabs, Proc. Soc. Exper. Biol. & Med. 57:186-187, 1954.

10. Pike, R. M.: The Isolation of Hemolytic Streptococci from Throat Swabs: Experiments with Sodium Azide and Crystal Violet in Enrichment Broth, Am. J. Hyg. 41:211-220, 1945.

11. Feldman, H. A., and Harmon, W.: Comparative Effectiveness of Direct Blood Agar and Modified Pike's Broth for Demonstrating Beta-Hemolytic Streptococci of Different Serological Groups, J. Lab. & Clin. Med. 40:297-302, 1952.

12. Commission on Acute Respiratory Diseases: Problems in Determining the Bacterial Flora of the Pharynx, Proc. Soc. Exper. Biol. & Med. 69:45-52, 1948.

13. Commission on Acute Respiratory Diseases: The Single Throat Culture as an Index of the Bacterial Flora of the Respiratory Tract, Am. J. Hyg. 50:168-174, 1949.

14. Kuroda, K., and Feldman, H. A.: A Simplified Modification of Pike's Broth, J. Lab. & Clin. Med. 49:142-144, 1957.

15. Rantz, L. A., and Randall, E.: A. Modification of the Technic for Determination of the Anti-Streptolysin Titer, Proc. Soc. Exper. Biol. & Med. 54:22-24, 1945.

16. Swife, H. F., in Bacterial and Mycotic Infections of Man, edited by R. J. Dubos, Philadelphia, J. B. Lippincott Company, 1952, p. 268.

17. Stollerman, G. H., and Rusoff, J. H.: Prophylaxis Against Group A Streptococcal Infections in Rheumatic Fever Patients: Use of New Repository Penicillin Preparation, J. A. M. A. 150: 1571-1575, 1952.

18. Chamovitz, R.; Catanzaro, F. J.; Stetson, C. A., and Rammelkamp, C. H.: Prevention of Rheumatic Fever by Treatment of Previous Streptococcal Infections: I. Evaluation of Benzathine Penicillin G, New England J. Med. 251: 466-471, 1954.

19. Diehl, A. M.; Hamilton, T. R.; Keeling, I. C., and May, J. S.: Long-Acting Repository Penicillin in Prophylaxis of Recurrent Rheumatic Fever, J. A. M. A. 155:1466-1470, 1954.

20. Peck, F. B., Jr., and Griffith, R. S.: Comparative Clinical Laboratory Studies of Penicillin-V and Penicillin-G, Antibiotics Ann., p. 506, 1956.

Staphylococcal Infections in Young Infants

Report of an Outbreak in a Hospital Nursery

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Outbreaks of pyogenic infection in newborn infants caused by penicillin-resistant strains of Staphylococcus are becoming a major problem. The purpose of this paper is to report such an outbreak which occurred in the newborn nursery at Freedmen's Hospital during the spring of 1957.

Nursery Facilities and Routines

The newborn nursery is designed to accommodate 10 premature and 35 full-term infants but is frequently filled beyond capacity. The turnover is rapid, the majority of full-term infants being discharged at the age of 3 days. The number of deliveries is approximately 250 per month. About 10% of all deliveries result in premature births.

There are two wards for obstetrical patients. On one of these a modified rooming-in procedure is used. The infant remains in his bassinet at the mother's bedside during the day but is returned to the nursery at night.

An individual bassinet with storage space for diapers, thermometer, etc., is provided for each infant. Babies are bathed on admission to the nursery but not thereafter except for cleansing the diaper area as needed. Dry dressings are applied to the cord stump.

All personnel entering the nursery are required to wear gown, cap, and mask. Hand scrubbing is required before handling an infant. Infected newborn infants are transferred to another ward for isolation.

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Clinical Résumé of Outbreak

Previous to the spring of 1957, pyogenic infection occurred sporadically and cross infection could be prevented by prompt isolation of infected infants. Between March and June, 1957, twenty newborn infants developed various types of pyogenic infection. These comprised about 2% of infants born during that period.

In 14 cases the infection developed in the nursery, and in 6 cases symptoms appeared within two weeks after discharge. Age at onset varied from 2 days to 2 months, the majority being less than 1 week of age.

Types of infection are listed below.

	Cases, No.
Conjunctivitis	5
Subcutaneous abscesses	5
Pyoderma	4
Parotitis	3
Septicemia	3
Mastitis	2
Omphalitis	2
Pneumonia with empyema	2
Pharyngitis	1
Cellulitis	1

There were six instances of multiple infection, as follows: (1) subcutaneous abscess and mastitis; (2) pyoderma and conjunctivitis; (3) pyoderma, subcutaneous abscess, and mastitis; (4) conjunctivitis and septicemia; (5) omphalitis, conjunctivitis, pneumonia, and empyema; (6) parotitis, pneumonia, and empyema.

The pyoderma consisted of superficial impetiginous lesions not extensive in distribution. Mastitis and parotitis were suppurative.

Bacteriological Studies

Staphylococcus (Micrococcus) pyogenes var. aureus, coagulase-positive, was isolated from the infected site in the 20 patients.

Phage Typing of Patients and Carriers

Phage Type	Patients	Well Infants	Personnel
52/42B/80/81	13	1	3
52/52A/80	3	12	5
52A/79			1
7/75			2
Untypable	1	2	2
Not typed	3	6	

All showed a similar pattern of antibiotic sensitivity, as follows: The organism was resistant to penicillin, streptomycin, chlortetracycline, oxytetracycline, tetracycline, and gantrisin. It was sensitive to chloramphenicol, erythromycin, novobiocin, and oleandomycin.

Organisms were further identified by bacteriophage typing in 17 of the 20 cases (Table). It appears that two strains predominate, 52/42B/80/81 and 52/52A/80.*

Treatment

Novobiocin (60 to 120 mg. per day) was administered to 12 patients either initially or as soon as results of antibiotic sensitivity studies were known. In three of these therapy was later changed to other antibiotics. Chloramphenicol (60 to 120 mg. per day) was used in three cases, and erythromycin (60 mg. per day), in one case. One case of conjunctivitis responded to chlortetracycline ophthalmic ointment, and one case of impetigo, to penicillin. All of the antibiotics to which the organism was sensitive were used at some time in the course of the two cases of pneumonia complicated by empyema. In these two cases fever was present for two to three weeks, while in the other patients it was never a prominent symptom. In two other patients recurrent subcutaneous abscesses necessitated readmission. At least four patients of the group were critically ill, but there were no deaths.

Infant Carriers

Beginning in May, nasal cultures were taken at one- to three-week intervals for four months from all premature infants. All of the initial cultures grew S. pyogenes var. aureus, coagulase-positive, with antibiotic sensitivity pattern and bacteriophage type similar to those of the infected infants. These infants and all subsequently admitted to the premature nursery were given novobiocin (80 mg. daily). This was continued for one month or until the time of discharge. During novobiocin prophylaxis all nasal cultures remained positive and all newly admitted patients became colonized in three to nine days. Two infants developed clinical infections while receiving novobiocin prophylaxis. Novobiocin was discontinued, and erythromycin (40 mg. daily) was administered for one month to all premature infants. Nasal cultures became negative for staphylococci within one week and remained so as long as erythromycin was given.

Two weeks after erythromycin was discontinued 4 of 18 premature infants again had positive nasal cultures.

Infections in Mothers

An increase in the incidence of postpartum breast abscesses was noted. None occurred in March or April, but during May and June eight women who had been delivered recently on our obstetrical service were readmitted to the surgical service with this diagnosis. Bacteriological studies on these cases are not available. The carrier state of their infants is not known. So far as we can determine, none of these women had infected infants.

Carriers Among the Nursery Personnel

Among 50 medical and nursing personnel there were 13 carriers of S. pyogenes var. aureus, coagulase-positive. The organism

* The method used by Dr. Martin Hicklin, of the National Institutes of Health, is outlined by him as follows: Phages used were 6, 7, 29, 47, 52, 3A, 3B, 3C, 52A, 42E, 54, 42D, 70, 75, 73, 79, 53, 42B, 80, 81, 39, 523, VA4, and 55. The lysis pattern listed is that obtained by the phage in routine test dilution (RTD) according to Blair,[3] although phage in 100 times the RTD was also used routinely. Phage 44A was not included in characterizing any of these strains because it was found inconsistent and difficult to interpret.

was found in the nose only in nine instances, in the throat only in two, and in both nose and throat in two. Antibiotic sensitivity tests were not done. Bacteriophage typing (Table) revealed three carriers of type 52/42B/80/81 and five carriers of type 52/52A/80. We found no permanent carriers.

Other Possible Sources of Infection

Plates were exposed in the nursery and delivery room. Cultures were taken from bedding, oxygen masks, and other equipment. No pathogens were found. The routine weekly cultures of milk formulas were negative.

Control Measures

Aside from attempts at antibiotic prophylaxis in the premature infants, there were no specific control measures. Infant skin care was not changed. A liquid detergent containing hexachlorophene was introduced for hand washing.

Comment

It is difficult to know what significance to attach to the presence of the ubiquitous Staphylococcus in the nose and throat. The carrier rate in healthy adults and children outside hospitals has ranged from 20% to 91% in various studies.[2-5] The higher figure was found by Cunliffe,[3] in young infants attending a well-baby clinic. Carrier rates among hospital personnel are higher than those among other adults in the community, and there is a higher percentage of pencillin-resistant strains.[5-8]

The multiplicity of strains makes it difficult to trace the source of an epidemic. Similar patterns of antibiotic sensitivity may help to establish the identity of a strain. Lysis of staphylococcal cultures by specific bacteriophages serves as another means of classification. Bacteriophages are not type-specific but tend to react with a number of strains. Patterns of bacteriophage susceptibility allow division of staphylococcal strains into six main groups. Organisms from a single outbreak have similar reaction patterns.[1]

In the past few years there have been many reports of staphylococcal infections in newborn nurseries.[9-20] In nine of these outbreaks the organism was resistant to penicillin, and in four, to the tetracyclines as well. Pyoderma was the commonest type of infection, but there were cases of mastitis, septicemia, pneumonia, and conjunctivitis. Breast abscesses in the mothers occurred in six of the epidemics.

The role of nursery personnel as carriers is considered an important factor by Baldwin.[21] He distinguishes between transient and permanent carriers. The former have been recently colonized by contact with infected or carrier infants. They can be cleared without treatment when the carrier state in the infants is eliminated. Permanent carriers, however, must be removed from contact with infants in order to control an epidemic. Wysham,[16] on the other hand, does not consider the nursery personnel as significant carriers of the epidemic strain.

High carrier rates in newborn infants have been reported in nonepidemic as well as epidemic periods.[3,21,23,24] Nasal cultures have been used to determine carrier status in most instances, but the skin and umbilical cord have been considered equally important.[23] The strains found in infants are more closely related to those of the personnel than to those of the mothers.[20,21,24]

Control measures for personnel carriers have included oxytetracycline cream,[7] neomycin-gramicidin ointment,[12] and neomycin-polymixin ointment [20] applied to the nares. Success in eliminating the carrier state was reported, but there were recurrences after treatment was discontinued.[7,20]

Control measures in infants have included hexachlorophene bathing,[10] chloramphenicol orally,[17] erythromycin orally,[20] hexachlorophene bathing plus erythromycin orally,[15] and bacteriocidal dyes applied to the cord stump.[22] Good results were claimed for all these methods.

In our series, novobiocin, to which the organism was sensitive and which produced an adequate result in treatment of some of the clinical infections, had no effect on the carrier state in the newborn. Erythromycin caused prompt disappearance of the carrier state; however, it can hardly be credited with termination of the epidemic, since that was already on the wane.

Summary

An outbreak of pyogenic infections involving 20 infants in a newborn nursery is described. The infecting organism was Staphylococcus pyogenes var. aureus, coagulase-positive. It was resistant to the commonly used antibiotics except novobiocin, erythromycin, chloramphenicol, and oleandomycin. Bacteriophage typing revealed two predominant strains, 52/42B/80/81 and 52/52A/80.

Sixteen per cent of the nursery personnel were carriers of the epidemic strains, as were one hundred per cent of the premature infants. Novobiocin given to the infant carriers did not eliminate the carrier state or prevent infection. Erythromycin eliminated the carrier state only while it was being administered to the infants. All of the infected infants recovered.

In 6 of the 20 infants who developed pyogenic disease, the infection did not become evident until after discharge from the hospital newborn nursery. It is readily apparent that nosocomial disease of this type may lead to outbreaks of infection in families and in the community at large. As an aid in controlling the sources and spread of this disease, all pyogenic infections in young infants should be made reportable by local health authorities. A comprehensive plan for the control of staphylococcal infections in the hospital and community has been recently outlined by Mudd.[25]

Dr. Martin Hicklin, Resident in Clinical Pathology, and Mr. Charles H. Zierdt, Bacteriologist, both of the Department of Clinical Pathology, National Institutes of Health, performed the bacteriophage typing.

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REFERENCES

1. Blair, J. E., and Carr, M.: Bacteriophage Typing of Staphylococci, J. Infect. Dis. 93:1, 1953.

2. Martin, T. D. M., and Whitehead, J. E. M.: Carriage of Penicillin-Resistant Staph. Pyogenes in Healthy Adults, Brit. M. J. 1:173, 1949.

3. Cunliffe, A. C.: Incidence of Staph. Aureus in the Anterior Nares of Healthy Children, Lancet 2:411, 1949.

4. Saint-Martin, M.: Incidence of Staphylococcal Carriers Among Healthy Children, Canad. J. Pub. Health 44:324, 1953.

5. Holloway, W. J., and Scott, E. G.: Studies on the Staphylococcus: II. Nasopharyngeal Carriers, Delaware M. J. 28:4, 1956.

6. Rountree, P. M., and Barbour, H. G.: Nasal Carrier Rate of Staphylococcus Pyogenes in Hospital Nurses, J. Path. & Bact. 63:313, 1951.

7. Gould, J. C., and Allan, W. S. A.: Staphylococcal Cross-Infection: Prevention by Treatment of Carriers, Lancet 2:988, 1954.

8. Loh, W., and Street, R. B.: Staphylococci in a Community Hospital: I. Nasopharyngeal Carrier Rate of Hospital Personnel on Maternity Wards and Antibiotic Sensitivity of Staphylococci Isolated, New England J. Med. 256:177, 1957.

9. Colbeck, J. C.: An Extensive Outbreak of Staphylococcal Infections in Maternity Units, Canad. M. A. J. 61:557, 1949.

10. Farquharson, C. D.; Penny, S. F.; Edward, H. E., and Barr, E.: Control of Staphylococcal Skin Infections in the Nursery, Canad. M. A. J. 67:247, 1952.

11. Miller, A. A.: An Outbreak of Pemphigus Neonatorum in the Maternity Department of a General Hospital with Special Reference to the Source of Infection, J. Obst. & Gynec. Brit. Empire 57:415, 1950.

12. Gillespie, W. A.; Pope, R., and Simpson, K.: Pemphigus Neonatorum Caused by Staphylococcus Aureus Type 71, Brit. M. J. 1:1044, 1957.

13. Feld, F., and Annungiata, D.: Staphylococcus Aureus Infection in the Newborn Infant, J. Pediat. 41:399, 1952.

14. Felsen, J.; Lapin, J.; Wolarsky, W.; Weil, A. J., and Fox, I.: Staphylococcal Infection in Hospital Nurseries and Pediatrics Wards, A. M. A. Am. J. Dis. Child. 81:534, 1951.

15. Shaffer, T. E.; Baldwin, J. N.; Rheins, M. D., and Sylvester, R. F.: Staphylococcal Infections in Newborn Infants: I. Study of an Epidemic Among Infants and Nursing Mothers, Pediatrics 18:750, 1956.

16. Wysham, D. N.; Mulbern, M. E.; Navarre, G. C.; LaVeck, G. D.; Kennan, A. L., and Gudt, W. R.: Staphylococcal Infections in an Obstetrical Unit: I. Epidemiologic Studies of

Pyoderma Neonatorum, New England J. Med. 257:295, 1957.

17. Webb, J. F.: Newborn Infections and Breast Abscesses of Staphylococcal Origin, Canad. M. A. J. 70:382, 1954.

18. Mathew, A. G., and Manessis, C.: Experiences with Staphylococcal Infections in a Maternity Hospital, M. J. Australia 2:781, 1956.

19. Battersby, E. T., and Stringer, H.: Pathogenic Staphylococci in a Maternity Annex, New Zealand M. J. 53:420, 1954.

20. Bass, J. A.; Stinebring, W. R.; Willard, C., and Felton, H. M.: Epidemiologic Study of a Hospital Outbreak of Micrococcic Infections, J. A. M. A. 166:731, 1958.

21. Baldwin, J. N.; Rheins, M. S.; Sylvester, R. F., Jr., and Shaffer, T. E.: Staphylococcal Infections in Newborn Infants: III. Colonization of Newborn Infants by Staphylococcus Pyogenes, A. M. A. J. Dis. Child. 94:107, 1957.

22. Jellard, J.: Umbilical Cord as a Reservoir of Infection in a Maternity Hospital, Brit. M. J. 1:925, 1957.

23. Edmunds, P. N.; Elias-Jones, T. F.; Forfar, J. O., and Balf, C. L.: Pathogenic Staphylococci in the Environment of the Newborn, Brit. M. J. 1:990, 1955.

24. Loh, W., and Aboig, A.: Staphylococci in a Community Hospital: II. Nasal Carrier Rate in Newborn Babies and Their Mothers, New England J. Med. 256:179, 1957.

25. Mudd, S.: Staphylococcic Infections in the Hospital and Community, J. A. M. A. 166:1177, 1958.

Prognosis in Neuroblastoma of Childhood

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The change in the medical attitude toward prognosis in neuroblastoma of childhood received its major impetus from the reports of Farber [1] and of Gross.[2] Subsequent publications from other centers [3-5] have amply confirmed the observation that there is a definite and significant long-term survival rate among the children with neuroblastoma. The magnitude of this survival rate appears to be influenced by several factors, among which age of the patient, presence of metastases, and degree of malignancy have been suggested.

The clinical experience at The University of Texas M. D. Anderson Hospital and Tumor Institute (MDAH), however, during the period from 1951 through 1957 disclosed what appeared to be consistently unsatisfactory end-results in 15 children with neuroblastoma (Table 1). Eleven of the fifteen were dead within nine months. Only one child was living and apparently free of disease four years after

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TABLE 1.—*Summary of Clinical Data in Children with Neuroblastoma, MDAH, 1951-1957*

Case	Sex	Age,* Yr.	Primary Site	Metastases *		Extent of Surgery	X-ray Therapy	Chemotherapy †	Present Status	Survival, Mo.‡
				Skeletal	Other					
1	M	2 3/12	Abdomen	Yes	Mediastinum, nodes, marrow	Cervical node biopsy	No	Act D, HN_2, St, Nit	Dead	4
2	M	2 3/12	Adrenal	No	None	Exploration & biopsy	Yes	No	Dead	4
3	M	3 4/12	Abdomen	Yes	Subcut., marrow	Biopsy of soft tissue mass	Yes	HN_2, B_{12}, TP	Dead	2
4	M	2 7/12	Adrenal	No	None	Exploration & biopsy	Yes	HN_2, B_{12}	Dead	3
5	F	7 3/12	Unknown	Yes	Nasopharynx, marrow	Biopsy of nasopharynx	Yes	HN_2, B_{12}, Ameth	Dead	5
6	M	2 10/12	Abdomen	No	Nodes	Exploration & biopsy	Yes	Act D, HN_2, B_{12}	Dead	4
7	M	3 6/12	?Thorax	No	Cerv. nodes	Excision	Yes	HN_2, Ameth	Dead	7
8	F	4 9/12	?Abdomen	Unknown	Pelvis	Exploration & biopsy	No	No	Dead	1
9	M	1 4/12	Unknown	No	Neck	Biopsy	Yes	No	Alive	48
10	M	1 4/12	Abdomen	Unknown	Nodes, bowels	Exploration & biopsy	Incomplete	No	Dead	2
11	M	4 8/12	Abdomen	Yes	Pelvis, lungs	Exploration & biopsy	Yes	No	Dead	8
12	M	14	Unknown	No	Nose	Biopsy	Yes	B_{12}, TP	Dead	9
13	M	3 7/12	Unknown	No	Roof of mouth	Excision	Yes	Act D, HN_2, Ameth, B_{12}	Living with disease	14
14	F	9/12	Abdomen	No	Nodes	Excision & nephrectomy	No	B_{12}	Alive	6
15	M	4 3/12	Abdomen	No	None	Excision	Yes	HN_2, B_{12}	Living with disease	5

* At time of diagnosis.
† Act D, actinomycin D; HN_2, mechlorethamine (nitrogen mustard); Nit, Nitromin (an oxidation product of mechlorethamine); B_{12}, vitamin B_{12} in massive doses; Ameth, amethopterin; TP, triethylene thiophosphoramide; St, steroids.
‡ From time of diagnosis.

diagnosis. Of three additional children who were still alive but in whom insufficient time had elapsed for adequate follow-up, two quickly had developed evidence of uncontrolled metastatic spread. Critical examination of the data on these patients has indicated subsequently that the seeming lack of therapeutic success could be attributed actually to the fortuitous overloading of the patient population by children in the older, unfavorable age group.

This experience initiated the present investigation, which was intended to evaluate systematically the various factors of prognostic significance in neuroblastoma. For this purpose, the accumulated clinical data reported in the recent literature from a number of different clinics were surveyed. The findings of that survey have been summarized in this paper.

Material

Data were obtained only from reports which were published in 1950 or later and which included clinical material on 10 or more patients. A search of the American literature yielded 15 such reports.[2,4-10] In combination with the M. D. Anderson Hospital experience, therefore, information became available on a total of 496 children with neuroblastoma (Table 2). The pooled sample was then studied to evaluate the possible relationship of selected factors (age, sex, site of primary tumor, presence of metastases, degree of cytologic differentiation, and therapy) to prognosis for long-term survival in children with neuroblastoma.

Results

Age.—In the evaluation of the relationship of age to prognosis in children with neuroblastoma, data on 292 patients under 15 years of age were used.* The patients were arbitrarily divided into two age groups: those 24 months or younger at the time of diagnosis and those over 24 months. Prognosis was measured in terms of survival for 14 months or longer following diagnosis. As shown in Table 2, there were 39.9% of children 24 months of age or younger with neuroblastoma who survived for 14 months or longer irrespective of therapy and other factors. In contrast to this, only 7.5% of children over the age of 2 years survived 14 months or longer. The data, therefore, showed with statistical

* References 2, 5-11, 14, and 15 and MDAH series.

TABLE 2.—*Age and Survival Data on Children with Neuroblastoma*

Source	Period of Study (or Date of Report)	Children Included in Report, No.			Incidence of 14 Mo. Survivors		
		Age 2 yr. & Under	Age Over 2 Yr.	Total	Age 2 yr. & Under	Age Over 2 Yr.	Total
Gross[5]*	Through 1940	?	?	57	?	?	11/57
	1940–1947	20	18	38	9/20	2/18	11/38
Phillips[4]	1932–1951	?	?	81	?	?	10/58
Horn et al.[6]	(1956)	29	15	44	16/27	0/14	16/41
Ackerman et al.[8]	1926–1949	4	5	9	1/3	2/5	3/8
Charache[7]	1937–1953	4	6	10	2/4	3/6	5/10
Oberkircher et al.[9]	1926–1951	8	12	20	2/8	0/12	2/20
Pack et al.[9]†	1931–1950	7	7	14	2/3	0/7	2/12
Poore et al.[10]	(1951)	5	11	16	2/5	0/9	2/14
Reiquam et al.[11]	1945–1954	20	5	25	5/20	0/5	5/25
Seaman et al.[12]	1949–1955	?	?	19	?	?	6/19
Snyder et al.[13]	1936–1950	?	?	31	?	?	3/24
Stowens[14]	(1957)	52	46	98	15/49	3/44	18/93
Uhlmann et al.[15]	(1955)	15	4	19	8/15	0/4	8/19
MDAH	1951–1957	3	12	15	1/2	0/10	1/12
Total				496	63/158	10/134	103/450

* Wittenborg's report[16] apparently utilized the same cases.
† It is not clear whether any of these cases were included in Phillips' report.[4]

TABLE 3.—*Relation of Sex of Patient with Neuroblastoma to Age Distribution, Frequency of Skeletal Metastases, and Incidence of Fourteen-Month Survivals*

	Patients, No.		
	Male	Female	Total
Age distribution			
2 yr. & under	52	43	95
Over 2 yr.	46	31	77
Frequency of skeletal metastases			
2 yr. & under	12/49	10/38	22/87
Over 2 yr.	21/43	14/27	35/70
Incidence of 14 mo. survivals			
2 yr. & under	20/35	14/30	34/65
Over 2 yr.	2/38	3/23	5/61

significance that the occurrence of 14-month survivals was not independent of age. Chances of survival were definitely good among those 2 years of age and younger and definitely poor in the older age group.

Sex.—The sex of the patients with neuroblastoma did not have any significant statistical relationship to age of patients, incidence of 14-month survival in each of two age groups, and frequency of skeletal metastases in each of two age groups (Table 3).

Site of Primary Tumor.—The anatomic site of the primary tumor was considered another variable of potential prognostic importance in neuroblastoma. Production of symptoms or development of mass in readily apparent areas could have led to earlier diagnosis. It was also conceivable that the anatomic location determined the ease and degree of therapeutic attack on the tumor. It was not known whether or not there were differences in malignant behavior among neuroblastomas arising in various parts of the body.

In 230 patients with neuroblastoma sufficient information had been included to permit evaluation of the anatomic distribution of tumors in relation to age.† Statistically these data showed that the anatomic distribution of the primary site of tumors appeared to be the same irrespective of the age group. To investigate the relationship between tumor site and survival, the incidence of 14-month survivors in children was tabulated for two anatomic divisions: "abdomen" and "extra-abdomen" (Table 4). It was concluded that on the basis of these comparisons the incidence of 14-month survivors was not significantly related to the site (abdomen or extra-abdomen) of the primary tumor.

Metastases.—The clinical behavior of most types of cancer has justified the assumption that the presence or absence of local and distant metastases influences survival. Wittenborg [16] has presented data to show that in neuroblastoma specifically there was a significant decrease in the rate of three-year survivals among those with demonstrable metastases at time of diagnosis as compared with the survival rate among those with no demonstrable metastatic lesions.

In the present study the pooled data were examined to evaluate, first, the relation of age to the incidence of metastases and, second, the relation of metastases to survival rate. Not all the published reports contained satisfactorily detailed clinical information. It was assumed, however, that, unless specifically stated, reasonably similar diagnostic procedures had been instituted in all patients.

From a total of seven studies‡ data on 138 patients were tabulated (Table 5). These figures indicated that a majority (73%) of the children already had evidence of metastases when first seen. The distribution of patients with metastases between the two age groups appeared to be at random. The occurrence of skeletal metas-

† References 5-10 and 15 and MDAH series.

‡ References 5, 7-10, and 15 and MDAH series.

TABLE 4.—*Relation of Site of Primary Tumor to Age and Fourteen-Month Survival*

	Patients, No.	
	Age 2 Yr. & Under	Age Over 2 Yr.
Primary tumor found in		
Abdomen	103	73
Thorax	16	10
Other	16	12
Incidence of 14 mo. survivals among patients with primary tumor in		
Abdomen	24/52	4/52
Extra-abdomen	11/17	3/17

TABLE 5.—*Frequency of Metastases at Time of Diagnosis and Relation of Metastases to Fourteen-Month Survivals and to Age of Patient*

	Patients, No.	
	Age 2 Yr. & Under	Age Over 2 Yr.
Patients with		
Skeletal metastases	18	33
Extraskeletal metastases	33	17
No metastases	22	15
Incidence of 14 mo. survival in patients with		
Skeletal metastases	2/16	3/32
Extraskeletal metastases	15/30	0/16
No metastases	16/22	2/12

tases, however, did show a significant relationship with age. The probability that the age distribution of skeletal metastases such as that shown in Table 5 occurred by chance alone is extremely small. These data, therefore, indicate that at the time of diagnosis skeletal metastases were found significantly more frequently among the older age group than among those 2 years of age and younger.

From the statistical evaluation of survival data two conclusions seem justified: 1. In the younger age group patients with extraskeletal metastases had the same survival rate as did those with no metastases. 2. Prognosis was uniformly poor among the older age group, irrespective of presence or absence of any type of metastases. These findings suggest, therefore, that other factors in addition to those related to presence or site of metastatic lesions must be considered in order to explain the difference in prognosis associated with age.

Therapy.—Published data did not permit satisfactory evaluation of the comparative effectiveness (measured as survival rates) of each of several methods of treatment in neuroblastoma. In many cases the lack of uniformity in the method of reporting clinical data made it impossible to relate such basic information as age, metastases, diagnostic procedures, and even types of therapy to the patients individually. The nature of the clinical data also indicated that the types of patients subjected to each form of therapy were not identical.

In spite of the heterogenous nature of the pooled data, it was believed that a significant superiority in effectiveness of any therapeutic program might become apparent from (*a*) study of result of therapy in cases where the existence of other factors made survival less likely, for example, older age group, presence of skeletal metastases, or cytologically more "malignant" tumors; (*b*) study of treatments used for children who have survived for long periods of time in spite of the existence of factors associated with poor prognosis, and (*c*) comparison of results in patients after attempts have been made to keep significant factors constant, for example, results in children under 2 years of age without demonstrable skeletal metastases.

Unfortunately, the 14-month survival rate among patients who were over 2 years of age or who had skeletal metastases at the time of diagnosis was much too small to permit satisfactory analysis.

The group of patients under 2 years of age and without skeletal metastases represented those who potentially had the most favorable chances for long-term survival. Tabulation of the pooled data (Table 6) showed that, of 52 patients who were placed in this category, 32, or 61.5%, survived for 14 months or longer, irrespective of the type of therapy. Among these, the children who received "no therapy" showed significantly lower survival rate than did those who received any form of therapy. Statistically, no differences in survival rate were apparent among those receiving surgical treatment alone, those receiving radio-

TABLE 6.—*Relation of Type of Therapy to Incidence of Fourteen-Month Survivals*

	Incidence of 14 Mo. Survivals	
Type of Therapy	Age 2 Yr. & Under with No Skeletal Metastases	Age Over 2 Yr. with No. Skeletal Metastases
No therapy	2/11	0/13
Surgery alone *	7/8	0/1
Radiation alone	11/19	2/12
Surgery plus radiation	11/13	0/2
Other therapy	1/1	0/0

* Both partial and complete removal of tumor has been included under "surgery"; biopsy was not considered to be surgical treatment.

therapy alone, and those receiving combined radiation and surgical therapy.

Even though definite conclusions regarding relative merits of different types of therapy could not be derived, examination of these data did permit certain generalizations: (*a*) Long-term survivals (three years or more) have followed the use of either surgical therapy alone or radiation therapy alone. (*b*) Long-term survivals without any radiation therapy have resulted from complete excision of tumor, partial excision of tumor, or even simple biopsy of tumor. (*c*) Though infrequently, long-term survivals have occurred in children over the age of 2 years and in children with skeletal metastases, irrespective of age. (*d*) Children under the age of 2 years with neuroblastoma had significantly higher survival rate, irrespective of type of treatment, than did the children over the age of 2 years.

Degree of Cytologic Differentiation.—Pathologists have emphasized the variability in the histologic appearance of different areas within the tumors in neuroblastomas.[2,14] In several reports, however, categorizations on the basis of cytologic characteristics have been attempted. These data were examined to see whether or not such classifications could be correlated with prognosis as measured by survival in children with neuroblastoma.

Material from four reports has been used.[5,6,10,14] The data on 167 patients were tabulated under a dichotomous classification: "relatively well differentiated" tumors and "relatively undifferentiated" tumors (Table 7). Malignant ganglioneuroma and ganglioneuroblastoma were included with the more differentiated group. The figures indicated that the occurrence of tumors of different cytologic characteristics was statistically unrelated to age. On the other hand, there was a highly significant statistical difference in the distribution of 14-month survivors among the differentiated and undifferentiated tumor groups in patients 2 years of age and younger. A significantly greater number of 14-month survivors were found among those with differentiated tumors and significantly fewer survivors were found among those with undifferentiated types of tumors. In patients over 2 years of age the survival rate was too small for satisfactory analysis.

TABLE 7.—*Relation of Cytologic Differentiation to Age and Fourteen-Month Survivals in Neuroblastoma*

	Patients, No.	
	Relatively More Differentiated Tumors	Relatively Less Differentiated Tumors
Age distribution		
2 yr. & under	26	64
Over 2 yr.	20	57
Incidence of 14 mo. survivals		
Age 2 yr. & under	18/24	16/60
Age over 2 yr.	3/18	2/34

Comments

Although various publications have emphasized the effectiveness of radiation,[4,16] of surgery,[5] and of combined surgical and radiation therapy[2,16] in the management of neuroblastoma in children, the pooled data proved unsatisfactory for comparative evaluation of different treatment modalities. Since the patients were not assigned randomly to treatment groups on the basis of a predetermined experimental design, the operation of selective factors could not be excluded. Thus, the "no treatment" category most probably included large numbers of patients in whom any palliative therapy was felt to be useless or in whom the progression of the disease led to death before institution or completion of definitive therapy. Again, localized tumors certainly would have been excised. In the presence of extensive local involvement or distant metastases radiotherapy probably received much stronger consideration than surgery. Radiotherapy in many cases appeared to have been added to the therapeutic program after the development of demonstrable metastases while the patient was under observation. Under these circumstances, therefore, it would seem that the group subjected to radiation with or

without surgical therapy was weighted disproportionately with patients in whom chances of prolonged survival were basically minimal. Not amenable to expression or to measurement were the intangible biases such as the medical attitudes and the parental and economic pressures that may have influenced the choice of therapy.

In the only comparison that seemed reasonably feasible (Table 6) the yields in terms of 14-month survivals among children 2 years of age and younger without skeletal metastases were statistically similar. Although Gross [2] has suggested that the combination of surgical and radiation therapy increases the survival rate, the present data did not demonstrate clear-cut superiority of any one therapeutic program. Percentage-wise the group receiving radiation alone scored the lowest. The figures, however, did not permit speculation concerning the chances of survival which the "radiation alone" group might have had if they had received surgery in addition to radiation. Existing evidence did not seem to warrant any conclusions regarding the influence of present-day chemotherapeutic techniques [17-19] on the long-term survival rate in neuroblastoma even though the clinical pattern of the disease may be altered to some extent.

This study also pointed out the continuing need for systematic definition of additional clinical indicators of biological behavior of neuroblastoma in children. Such considerations as duration of symptoms, size of tumor, presence of metastases, and rating from histologic appearance have proved useful only to a limited degree in the assessment of the status of the malignant disease in the patient. With the increasing use of chemical agents of antineoplastic potentialities the results of therapy must be measured not only in terms of duration of survival but also in terms of degree of palliation.

The striking relationship of age to survival raised some provocative questions. At the time of initial work-up skeletal metastases were found more frequently in the older age group. The age differential in survival rate persisted among those without demonstrable osseous lesions. Once skeletal metastases had occurred the prognosis for survival was poor, irrespective of age. Was there, then, an increased propensity for the malignant disease to spread to the bones in the older patients? If clinical malignancy of neuroblastoma is a function of time,[20,21] then it might be speculated that at the time of diagnosis the malignant disease would have existed for a longer period in the older child than in the younger child. Neuroblastoma in the older child, therefore, could have represented a more "advanced stage" in its natural evolution. Shimkin [22] has shown in his studies of the natural history of certain types of neoplastic disease in man that per cent survivals decreased rapidly with duration from apparent onset. Although neuroblastoma was not included in Shimkin's study, a similar type of survival curve might have been expected.

Summary

Clinical summaries on 15 children with neuroblastoma are presented.

From a study of pooled data on 496 cases of neuroblastoma the relationship of various factors (age, sex, site of primary tumor, metastases, cytologic differentiation, and therapy) to prognosis for long-term survival is evaluated. Age over 2 years, presence of skeletal metastases, and cytologic undifferentiation were associated with poor survival rates. No differences in therapeutic effectiveness among radiation alone, surgery alone, and combined surgery plus radiation were noted.

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REFERENCES

1. Farber, S.: Neuroblastoma, Am. J. Dis. Child. 60:749, 1940.

2. Gross, E.: Surgery of Infancy and Childhood, Philadelphia, W. B. Saunders Company, 1953, p. 606.

3. Beck, S. M., Jr., and Howard, P. J.: Neuroblastoma: Review of the Literature and Report of 6-Year Cure by Roentgen Therapy, A. M. A. Am. J. Dis. Child. 82:325, 1951.

4. Phillips, R.: Neuroblastoma, Ann. Roy. Coll. Surgeons 12:29, 1953.

5. Horn, R. C., Jr.; Koop, C. E., and Kiesewetter, W. B.: Neuroblastoma in Childhood: Clinicopathologic Study of 44 Cases, Lab. Invest. 5:106, 1956.

6. Ackerman, L. V., and Taylor, F. H.: Neurogenous Tumors Within the Thorax: A Clinicopathological Evaluation of 48 Cases, Cancer 4: 669, 1951.

7. Charache, H.: Tumors in Children, New York J. Med. 54:1775, 1954.

8. Oberkircher, O. J.; Staubitz, W. J., and Parmenter, F. J.: A Clinical Study of Neuroblastoma, J. Pediat. 43:177, 1953.

9. Pack, G. T.; Horning, E. D., and Ariel, I. M.: Neuroblastoma (Sympathicoblastoma) with an Analysis of 14 Cases and a Survey of the Literature, J. Neuropath. & Exper. Neurol. 11: 235, 1952.

10. Poore, T. N.; Dockerty, M. B.; Kennedy, R. L. J., and Walters, W.: Symposium on Surgical Aspects of the Cancer Problem: Abdominal Neuroblastomas, S. Clin. North America 31:1121, 1951.

11. Reiquam, C. W.; Beatty, E. C., Jr., and Allen, R. P.: Neuroblastomas in Infancy and Childhood: A Review of 10 Years' Experience, A. M. A. J. Dis. Child. 91:588, 1956.

12. Seaman, W. B., and Eagleton, M. D.: Radiation Therapy of Neuroblastoma, Radiology 68:1, 1957.

13. Snyder, W. H., Jr.; Kruse, C. A.; Greaney, E. M., and Chaffin, L.: Retroperitoneal Tumors in Infants and Children: Report of 88 Cases, A. M. A. Arch. Surg. 63:26, 1951.

14. Stowens, D.: Neuroblastoma and Related Tumors, A. M. A. Arch. Path. 63:451, 1957.

15. Uhlmann, E. M., and von Essen, C.: Neuroblastoma (Neuroblastoma Sympatheticum), Pediatrics 15:402, 1955.

16. Wittenborg, M. H.: Roentgen Therapy in Neuroblastoma: A Review of 73 Cases, Radiology 54:679, 1950.

17. Franklin, J. E.: Analysis of Cancer in Infancy and Childhood, New York J. Med. 53: 1659, 1953.

18. Farber, S.; Toch, R.; Sears, E. M., and Pinkel, D.: Advances in Chemotherapy of Cancer in Man, Advances Cancer Res. 4:2, 1956.

19. The Treatment of Neuroblastoma with Vitamin B_{12}, British Empire Cancer Campaign Report, London, 1954, p. 199.

20. Collins, V. P.; Loeffler, R. K., and Tivey, H.: Observations on Growth Rates of Human Tumors, Am. J. Roentgenol. 76:988, 1956.

21. Stewart, F. W.: Factors Influencing Curability of Cancer, in Third National Cancer Conference Proceedings, Philadelphia, J. B. Lippincott Company, 1957, p. 62.

22. Shimkin, M. B.: Natural History of Neoplastic Disease, cited by Homburger, F.: The Biologic Basis of Cancer Management, New York, Paul B. Hoeber, Inc. (medical book department of Harper & Brothers), 1957, p. 155.

Chronic Renal Disease in Children

Correlation of Clinical Findings with Morphologic Characteristics Seen by Light and Electron Microscopy

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Although more than 100 years have elapsed since Richard Bright's classic description of a group of nonsuppurative renal diseases, neither our understanding of the etiology and pathogenesis nor the methods of treatment for these diseases have improved appreciably.

With concepts presently available the clinician faced with a patient suffering from a chronic renal disease finds diagnostic criteria, classification, basis for prognosis, and method of treatment completely inadequate. For example: Are acute and chronic glomerulonephritis the same disease, and, if not, how are the etiologic and pathogenic mechanisms of the two diseases related or different? Where in the spectrum of renal disease is the nephrotic syndrome properly assigned? Is anaphylactoid purpura with nephritis a form of acute glomerulonephritis, as some have proposed, or does this syndrome belong in the group of diffuse vascular diseases of which disseminated lupus erythematosus and polyarteritis nodosa are examples?

In an attempt to gain information regarding these questions and insight into the etiology, the pathologic classification, and the pathogenesis of chronic renal disease in childhood, we have undertaken an extensive clinical, laboratory, and pathologic study of a group of children ill with these various diseases. Included in this investigation is a study of the pathology of the kidney by renal biopsy in each of the children and, where feasible, at selected intervals through the course of the disease.

The purpose of this paper is to present the preliminary observations on the pathology of the early renal lesions in a variety of chronic renal diseases, as revealed by renal biopsy, studied both by light microscopy and by electron microscopy, and to correlate these observations with clinical findings.

Materials and Methods

We have thus far had the opportunity to study 72 kidney biopsy specimens from 58 children with diffuse renal disease. Included are children suffering from anaphylactoid purpura, disseminated lupus erythematosus, acute glomerulonephritis, subacute and chronic glomerulonephritis, and the nephrotic syndrome (Table 1).

Kidney biopsy specimens have been obtained by both the technique of surgical exploration and removal of a wedge biopsy and by needle biopsy, with use of the Vim-Silverman biopsy needle.

A portion of each biopsy specimen was fixed in formol-saline solution, dehydrated, embedded, and sectioned by the usual technique for light microscopy. All tissues were stained with hema-

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TABLE 1.—*Renal Biopsy in Diffuse Renal Vascular Disease in Children*

Clinical Diagnosis	Cases, No.	Adequate Biopsy Specimens, No.
Anaphylactoid purpura	8	9
Lupus erythematosus	5	9
Glomerulonephritis	14	17
Nephrotic syndrome	31	37
Totals	58	72

toxylin and eosin, azocarmine, and modification of the periodic acid (Schiff) methods.

Other portions of the biopsy specimen were cut into approximately 1 mm. cubes, fixed in 1% buffered osmic acid,[1] dehydrated through serial alcohols, embedded in *n*-butyl methacrylate,[2] and sectioned on a Servall, Porter-Blum microtome,[3] equipped with a plate-glass knife.[4] Sections of 200 to 500 A. in thickness were mounted on copper specimen grids and examined in an RCA EMU-2b electron microscope with a biased gun, 30μ objective aperture, and a 10 mil condenser aperture. Sections of 1μ to 2μ were also prepared, mounted on glass slides, and stained with either hematoxylin or gallocyanin-azophloxine stains for light microscopy.[5] Thus it was possible to study the same glomeruli by light and by electron microscopy. Details on the techniques used in tissue preparation and sectioning of the tissues for electron microscopic study are available elsewhere.[6]

Biopsy Techniques

The surgical biopsies were performed by members of the Department of Urology of the University of Minnesota. The kidney was approached from the flank posteriorly and exposed, and a small wedge of cortex was excised.

Percutaneous needle biopsy of the kidney was performed with the patient in the prone position, as described by Muehrecke et al.[7] Procaine, 1%, was used as the local anesthetic in all cases. Adapting the needle biopsy technique to the study of kidney pathology in children presented many technical problems. Very young children (under 2 years) are usually poor candidates for needle biopsy, since their capacity for cooperation is limited and since the small size of the kidney makes successful biopsy difficult. The percentage of adequate biopsy specimens obtained in the very young children is consequently low. Since we considered the risk of needle biopsy of the kidney in very young children to be potentially greater than the risk in older children, we have elected to use the technique of open surgical biopsy for the study of children under 2 years of age.

Although it has been somewhat more difficult to obtain renal biopsy specimens from very edematous or obese children, adequate biopsy specimens have been obtained from most nephrotic children in whom the attempt has been made. Severe ascites and anasarca increase the difficulty of localization of the kidney and the appreciation of its depth. We believe that part of the difficulty encountered in the very edematous child may be related to the excess mobility of the kidney, which permits the organ to move away from the advancing biopsy needle.

Another problem which has been encountered concerns needle biopsy of the kidney which is bound to the dorsal fascia by adhesions developed as a complication of previous surgical renal biopsy. Under this circumstance it has been difficult to appreciate the true depth of the kidney and deeper puncture of the kidney than is desirable has resulted.

A satisfactory renal biopsy specimen is a cylinder of renal parenchyma approximately 1.5 cm. in length and 0.5 mm. in diameter (Fig. 1). A good specimen usually contains 15 to 30 glomeruli and associated tubules. We have considered the specimen adequate for study if 10 glomeruli and associated tubules were obtained. According to these criteria, we have obtained adequate biopsy specimens in approximately 70% of attempts by the needle biopsy technique in children.

The question of adequacy of the biopsy specimen as a reflection of the histological state of the total renal parenchyma is of crucial importance. Postmortem studies of the kidney in the renal diseases with which we are concerned in this report have revealed the lesion to be sufficiently diffuse in its distribution and uniform in its character to permit consideration of the biopsy specimen as being representative of the existing pathology. In the first place, necropsy studies of the kidneys from patients with these diffuse renal diseases show the disease process to be diffuse and uniform throughout the renal cortex. Experience has shown that the chances are slim indeed that a biopsy specimen containing at least 10 glomeruli would fail to reveal the characteristic pathology. Secondly, comparison of the kidney biopsy specimens from 10 children in the present study with sections of the kidney from the same children obtained at autopsy a few weeks after the biopsy have consistently demonstrated excellent agreement in the two specimens in both the type and the

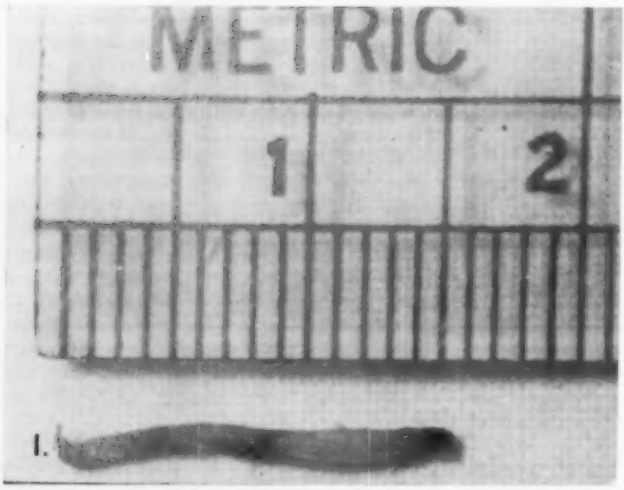


Fig. 1.—A cylinder of kidney tissue about 1.5 cm. in length is shown. This is a typical adequate needle biopsy specimen.

severity of the pathology involved. Finally, we have confirmed the observation of Muehrcke et al.[8] that interpretations of multiple postmortem needle biopsies of the kidney studied and read without knowledge of the autopsy diagnosis are in excellent agreement with one another and with the interpretations of the histopathology indicated by the usual pathological specimens.

Complications of Needle Biopsy of the Kidney

Although the risk of open surgical biopsy of the kidney is probably only slightly greater than the risk of general anesthesia alone, this procedure is associated with the pain and discomfort of an incision and with prolongation of the interval of hospitalization by at least one week.

The risk of needle biopsy technique has not been completely defined, but we have been impressed with the safety and facility of this procedure in children. Thus far in our series no deaths can be attributed to the biopsy technique, and the morbidity associated with needle biopsy of the kidney is generally nil. In the occasional case where difficulty is encountered it is attributable to hemorrhage either into the perirenal tissues or into the renal pelvis. Careful study of the bleeding and clotting phenomena in the candidate is essential if the risk of needle biopsy is to be kept low.

Two instances of significant complications following more than 100 attempts at needle biopsy of the kidney in children have been observed in the present series. One child developed pain at the biopsy site and was observed to have a decline of 2 gm. % in his hemoglobin level after a successful renal biopsy. X-ray and clinical evidence suggested a diagnosis of a perirenal hematoma. The bleeding stopped spontaneously; the blood loss was replaced with a small transfusion, and no significant late sequelae of this complication have been observed. Another child developed prolonged, persistent, gross hematuria three days after a renal biopsy. The hematuria was associated with the development of anemia, pain, and temporary occlusion of pelvis and ureter of the biopsied kidney by blood clots. Complete recovery and return of normal renal function followed repeated transfusions of fresh whole blood collected by gravity in siliconized equipment, and no late sequelae of this complication have been noted.

Six additional children in the series have had gross hematuria of short duration. Gross hematuria is usually associated with deep biopsy of the kidney, in which case

the specimen often is composed of either renal tubules alone or of renal tubules in combination with a fragment of the renal pelvic mucosa. Deep biopsy of the kidney should be avoided in order to minimize the incidence of gross hematuria as a complication of the technique.

In order to evaluate the effect of needle biopsy upon renal function, as measured by renal clearance of creatinine, inulin, and *p*-aminohippurate, renal-clearance studies with these materials were performed before and after renal biopsy in eight children. No significant alteration of renal function was demonstrated to occur as a result of kidney biopsy.

This technique, in our studies, has proved to be an atraumatic procedure, associated with minimal pain, and with a low incidence of complications. Our studies also indicate that serial renal biopsies are feasible and are not associated with a significantly increased hazard. Despite the obvious limitations noted above, we believe that the procedure deserves extensive use as an investigative technique in the study of renal disease in childhood.

Observations

The Nephritis of Anaphylactoid Purpura

Anaphylactoid purpura (Henoch-Schönlein's disease) is a syndrome characterized by nonthrombopenic purpura, arthritis or arthralgia, gastrointestinal pain and/or bleeding, and a form of glomerulonephritis. The occurrence of nonthrombopenic purpura together with chronic renal disease was first recognized by Osler.[9]

Some degree of renal involvement manifested by an abnormal urinalysis is present in 30% to 50% of the cases.[10-13] In a series of 25 cases of anaphylactoid purpura which we have recently studied,[14] 17 of the children had renal involvement as determined by abnormal Addis counts of a 12-hour urine specimen.

The significance and prognosis of the glomerulonephritis which occurs in anaphylactoid purpura are disputed. Several authors have reported spontaneous and complete recovery in a majority of cases [10,15]; however, Osler's experience was grim, and Wedgewood [12] emphasized recently that the "subacute glomerulonephritis" which occurred in 9 of his 36 cases persisted as long as two years. Derham and Rogerson [16] recently reported that 11 of 17 children followed 5 to 10 years had clinical evidence of glomerulonephritis.

Although the etiology of anaphylactoid purpura is not known, there is evidence to suggest that the disease may be a function of an abnormal immune response involving capillary components.[17] Hypersensitivity to β-hemolytic streptococcal infection has been suggested as an etiologic factor,[18] and the nephritis of anaphylactoid purpura is believed by some investigators to be simply a variant of acute glomerulonephritis. The few morphologic descriptions of the renal lesion obtained from autopsy study have characterized the process as a form of subacute glomerulonephritis.[19,20] In fatal cases a generalized arteriolitis involving the small vessels of the heart, adrenal glands, and kidneys has also been described.[20]

During the past two years, we have obtained renal biopsy specimens from eight children with anaphylactoid purpura. Data describing this material are summarized in Table 2. During the course of the anaphylactoid purpura, six of the children had a markedly abnormal urinalysis, reflecting the underlying nephritis. In each instance, except Case 2, the urinary abnormalities were first noted when the general manifestations of the disease became apparent. In Case 2 the renal disease first appeared two months after the onset of purpura and arthritis. Renal biopsy specimens were obtained at intervals after the onset of the renal disease, varying from two weeks (Case 2) to six and one-half years (Case 5). In Cases 3, 4, and 5 there was clinical and laboratory evidence of a decrease in the severity of the nephritis, or "healing" of the renal lesion, at the time of the biopsy. Cases 6 and 7 represent instances in which

TABLE 2.—*Renal Biopsy in Anaphylactoid Purpura*

Case	Age, Yr.	Duration at Biopsy	Laboratory Results, Acute Illness: Urinalysis * Alb.	Urinalysis * RBC	ASO Titer †	Pathology ‡
1	7	5 mo.	2+	Gross	< 50	"Segmental" nephritis
2	4	4 mo.	1+	3+	100	"Segmental" nephritis
3	6 7	17 mo. 2½ yr.	3+ 0	Gross 0	125	"Segmental" nephritis Normal
4	13	4 yr.	1+	2+	500	Normal
5	17	6½ yr.	3+	Gross	200	Healed "segmental" nephritis
6	5	15 mo.	0	0	< 50	Normal
7	12	2 mo.	0	0	125	Normal
8	5	2 mo.	1+	2+	< 50	Normal

* Alb., urinary albumin, graded 1 to 4+; RBC, hematuria, graded 1 to 4+.
† ASO titer, antistreptolysin O antibody titer in Todd units per millimeter.
‡ "Segmental" nephritis, see text.

typical anaphylactoid purpura occurred, and renal biopsy specimens were obtained in the absence of urinary abnormality. No evidence of renal involvement has subsequently been observed in these two children. A second kidney biopsy specimen was obtained in Case 3, one year after she had apparently completely recovered from her disease.

Illustrative Case Reports—Anaphylactoid Purpura

CASE 1.—A 7-year-old white boy developed abdominal pain in September, 1955. Surgical exploration was undertaken, and a hemorrhagic area in the terminal ileum was noted. Forty-eight hours later he was noted to have edema of the legs and a flat reddish-brown rash over the buttocks and lower extremities, which later was described as purpuric; 4+ albuminuria and 1+ erythruria were noted on urinalysis. He continued to have intermittent purpura, abdominal pain, arthralgia, and gross hematuria during the subsequent five months. Albuminuria and microscopic hematuria were always present on urinalysis. His renal function remained normal. A biopsy specimen of the kidney in this patient was obtained in February, 1955, five months after the onset of anaphylactoid purpura and nephritis. The glomeruli appeared somewhat enlarged and hypercellular. The most constant abnormality noted was focal glomerular capillary occlusion by hyaline material with the morphologic and tinctorial characteristics of fibrinoid. We have termed these morphologic changes segmental nephritis (Fig. 2).

CASE 3.—A 6-year-old girl developed painful swelling of the hands, ankles, and knees and a

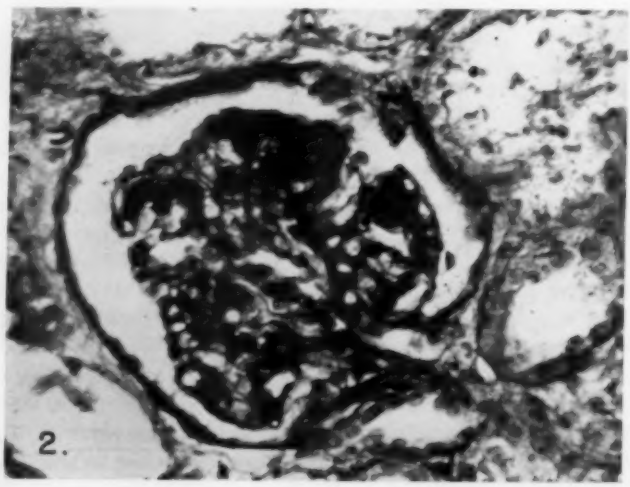


Fig. 2.—A typical involved glomerulus in the acute stage of the renal disease of anaphylactoid purpura (Case 1, Table 2). A focal accumulation of fibrinoid material is shown in one lobule of the glomerulus. Periodic acid-Schiff stain; × 400.

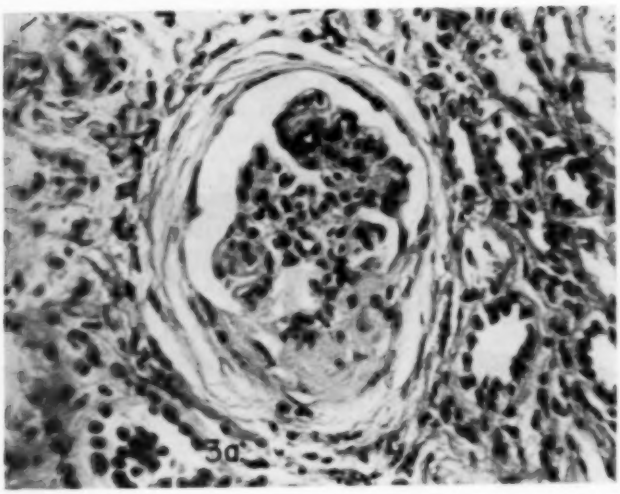


Fig. 3a.—Focal scarring and hypercellularity in a glomerulus from a child with anaphylactoid purpura (Case 3, Table 2). A crescent is visible in the lower half of the glomerulus, and thickening of Bowman's capsule is evident. Hematoxylin and eosin stain; ×300.

red maculopapular rash over the lower extremities and buttocks in September, 1954. These findings recurred intermittently over the following two months. In November, 1954, gross hematuria, abdominal pain, epistaxis, and hematemesis were noted. Albuminuria and hematuria were present in every urine specimen examined over the next 15 months. Her renal function was reduced to about 60% of normal at the time of the renal biopsy, in February, 1956, seventeen months after the onset of her disease.

The striking glomerular alteration observed in the biopsy specimen was segmental glomerular capillary hyalinization and fibrosis, with focal obliteration of the capillary channels. This lesion would appear to be a more chronic stage of the process observed in the more acute cases of anaphylactoid purpura with nephritis (Fig. 3a).

Because of the severity of the clinical and morphologic manifestations of the renal disease in this child, intensive corticosteroid therapy was instituted and was continued for one month. All signs of renal involvement in this child subsequently disappeared, and a second renal biopsy, performed in July, 1957, revealed normal architecture by light microscopy (Fig. 3b).

Case 5.—A boy developed gross hematuria, fever, and severe abdominal pain in October, 1949. Intermittent gross hematuria and constant microscopic hematuria were noted over the next four months. In January, 1950, a red maculopapular rash appeared over the legs and buttocks. Early

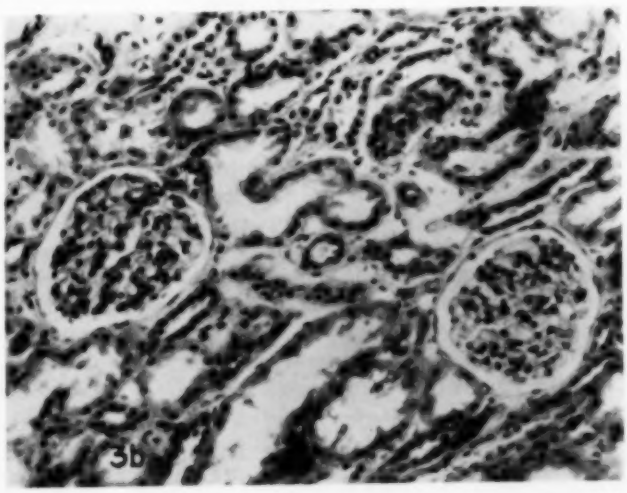


Fig. 3b.—Normal glomerular structure. Second biopsy specimen from Case 3, Table 2, obtained 17 months after the first. Hematoxylin and eosin stain; ×110.

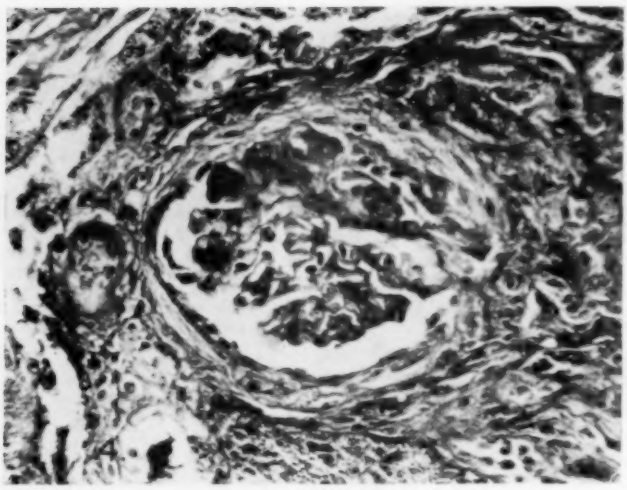


Fig. 4.—Severe segmental fibrosis in a glomerulus from a child with anaphylactoid purpura (Case 5, Table 2). The interstitial tissue surrounding the glomerulus is also very fibrotic. Azocarmine stain; × 300.

in the disease there was clinical evidence of renal insufficiency with retention of nitrogen (BUN, 78 mg. %). His renal function subsequently improved, despite recurrent attacks of gross hematuria and constant albuminuria and microscopic hematuria through the next five and one-half years. The last bout of macroscopic hematuria occurred in October, 1955. At the time of the renal biopsy, in March, 1956, six and one-half years after onset of the disease process, the Addis count of a 12-hour urine specimen was normal. Discrete renal-function tests at that time were also normal.

Microscopic sections of the biopsy specimen revealed normal glomeruli except for an occasional scarred, fibrotic segment manifested by adhesion to the capsular epithelium and coalescence and obliteration of segments of the glomerular capillary network. These changes were evident in sections stained with azocarmine. This abnormal morphology would appear to represent the healed stage of glomerulonephritis of anaphylactoid purpura (Fig. 4).

Comment

The severity and chronicity of the pathologic renal manifestations of the glomerulonephritis of anaphylactoid purpura vary widely from case to case; however, the basic morphologic abnormality appears to be similar in all the cases which we have studied.

The acute glomerular lesion is characterized by segmental glomerular proliferation and occlusion of capillaries by Schiff-positive fibrinoid material. Chronologically older lesions appear as segmental areas of organized hyaline material or as frank segmental scars of fibrous tissue.

Evidence in Case 3 suggests that the acute renal vascular lesion of anaphylactoid purpura is reversible and that restoration of an involved glomerulus to normal may occur. If this is true, it seems likely that healing is associated with removal of the fibrinoid material prior to its organization into a hyaline-fibrous complex which renders that portion of the glomerulus nonfunctioning. This observation suggests that it may be possible to develop methods of treatment which will result in cure of the renal lesion of anaphylactoid purpura. Research designed to determine the mechanisms involved in the pathogenesis of the renal lesion in this disease are thus likely to be rewarding.

Present morphologic studies indicate that the renal lesion of anaphylactoid purpura is not related closely to the renal lesion of acute glomerulonephritis. This observation is compatible with most clinical studies, which indicate that cases of anaphylactoid purpura are not associated with preceding infection with nephritogenic strains of β-hemolytic streptococci. Further support for the theory that acute glomerulonephritis and anaphylactoid purpura have different etiologic mechanisms is offered by im-

munologic studies, which reveal high levels of antistreptococcal antibodies in patients with recent acute glomerulonephritis, whereas such antibody titers in patients with anaphylactoid purpura are usually normal.[14,21]

The morphologic studies based on light microscopy correlated with the available clinical data suggest that the nephritis of anaphylactoid purpura is a diffuse vascular disease, resulting in pathologic renal lesions which resemble the renal lesion of disseminated lupus erythematosus. It is proposed that anaphylactoid purpura be classified as a member of the group of diffuse vascular fibrinoid diseases.

Disseminated Lupus Erythematosus

Disseminated lupus erythematosus (D. L. E.) is a severe diffuse chronic vascular disease characterized by prolonged intermittent fever, recurrent involvement of the synovial and mucous membranes, various erythematous skin eruptions, leukopenia, and glomerulonephritis. The glomerulonephritis of D. L. E. is manifest by albuminuria, microscopic hematuria, and, frequently, some degree of renal insufficiency.

Adrenocorticotropic hormone (ACTH) and cortisone have often proved to be effective in the control of the acute systemic manifestations, but there is as yet no evidence that these drugs alter the course or the manifestations of the renal disease.[22] Dubois[23] has shown, however, that some transient clinical and laboratory improvement of the renal disease in D. L. E. may follow prolonged therapy with the adrenal steroids.

The renal pathology in a typical case of D. L. E. is characterized by a glomerulitis with thickening of the capillary membranes. The thickened glomerular capillary wall has been likened to a wire loop, and this change is considered to be the characteristic renal lesion.[24]

In many cases of D. L. E. with clinical renal involvement, however, the kidney pathology present at autopsy is described as compatible with subacute or chronic glomerulonephritis and the typical "wire loops" are not present. Recent studies of biopsy specimens of the kidney in adult patients with D. L. E. has revealed a multiplicity of pathologic changes.[25]

Five children in whom the diagnosis of D. L. E. was established have been studied by renal biopsy. Table 3 lists the pertinent data from these patients. These children have a nephritis characterized by proteinuria, abnormal Addis counts, and reduced renal function in three instances. Serial renal biopsy specimens were obtained in three cases during prolonged intensive steroid therapy.

The duration of the disease at the time of the initial biopsy varied from three months

TABLE 3.—*Renal Biopsy in Disseminated Lupus Erythematosus*

Case	Age, Yr.	Duration of Disease at Biopsy	Urinalysis *		BUN,† Mg. %	Discrete Renal Function,‡ %		Characteristic L. E. Cells §	Pathology by Light Microscopy
			Alb.	RBC					
1	16	3 yr.	2+	2+	46	C_i	30	Present	Chronic glomerulonephritis
2	16	4 mo.	1+	3+	21	C_i	100	Present	Proliferative glomerulonephritis
		10 mo.	Tr	1+	16	C_u	106	Absent	Minimal proliferative glomerulonephritis
	17	15 mo.	Tr	0	9			Absent	Normal
3	16	20 mo.	1+	2+	12	C_i	76	Present	Segmental proliferative glomerulonephritis
		31 mo.			13	C_c	80	Absent	Normal
4	15	3 mo.	1+	2+	27	C_i	60	Present	Mod. proliferative glomerulonephritis
		12 mo.	Tr	2+	20			Absent	Mod. proliferative glomerulonephritis with wire loops
5	14	3½ yr.	2+	2+	21			Absent	Mod. proliferative glomerulonephritis with wire loops

* Alb., urinary albumin, graded 1 to 4+; RBC, hematuria, graded 1 to 4+.
† BUN, blood urea nitrogen.
‡ C_i, renal clearance of insulin; C_u, renal clearance of urea; C_c, renal clearance of creatinine. Per cent of normal value indicated.
§ L. E. cells, characteristic cells described in blood and bone marrow of patients with disseminated lupus erythematosus.

in Case 4 to three years in Case 1. All patients except Case 5 were treated with pituitary-adrenal hormones in large doses, beginning shortly after onset of the disease. In each instance marked clinical improvement occurred after onset of steroid therapy but there was no evidence at the time of the kidney biopsy of improvement in the renal disease as determined by urinalysis, serum chemistry studies, or renal-function studies. In Case 1 clinical signs of severe renal insufficiency had developed by the time the kidney biopsy was performed.

Case Reports — Disseminated Lupus Erythematosus

CASE 1.—A 13-year-old boy developed fever, multiple painful swollen joints, a mottled rash about the face, and chest pain in July, 1953. The diagnosis of disseminated lupus erythematosus was established in March, 1954. At that time moderately severe renal involvement was suggested by the urinary excretion of 40,000,000 red blood cells, 25,000,000 white blood cells, 3,000,000 casts, and 1.8 gm. of protein in a 12-hour specimen. A urea-clearance study at this time was found to be 40% of normal (32 cc. per minute). The blood urea nitrogen was 25 mg. %. Blood pressure was 130/90 mm. Hg.

The patient was given large doses of cortisone during the subsequent two years and remained in clinical remission. Severe hypertension developed, which resulted in his readmission to the hospital in March, 1956. At this time there was evidence of progressive deterioration of renal function in that the glomerular filtration rate was 23% of normal (inulin clearance, 28 cc. per minute per 1.73 square meters surface area). The urinary sediment was essentially unchanged from the previous studies.

A needle biopsy of the kidney was performed at that time. Glomerular enlargement, extensive endothelial proliferation, and numerous epithelial crescents were observed microscopically. The tubules were atrophic, and an associated pronounced interstitial cellular infiltration and fibrosis were evident (Fig. 5).

Renal insufficiency accompanied by hypertension and uremia progressed over the next four months, and the patient died in July, 1956.

The microscopic sections of the kidneys obtained at autopsy revealed no changes significantly different from those described in the kidney tissue which had been studied five months earlier.

CASE 2.—A 15-year-old girl was well until about October, 1955, when she developed high fever and painful swelling of the hands, knees, ankles, and elbows. A maculopapular erythematous rash appeared over her nose and cheeks shortly thereafter. Intermittent fever, joint pain, severe menorrhagia, and epistaxis prompted her admission to the University of Minnesota Hospitals in November, 1955.

She was found to have severe anemia, leukopenia, thrombocytopenia, albuminuria, and microscopic hematuria. Numerous cells typical of disseminated lupus erythematosus were found in the peripheral blood and bone marrow.

Clinical remission followed treatment with large doses of cortisone. The abnormal urinary sediment persisted. A 12-hour urine specimen contained 154,000,000 red blood cells, 14,000,000 white blood cells, 4,000,000 casts, and 1.4 gm. of protein.

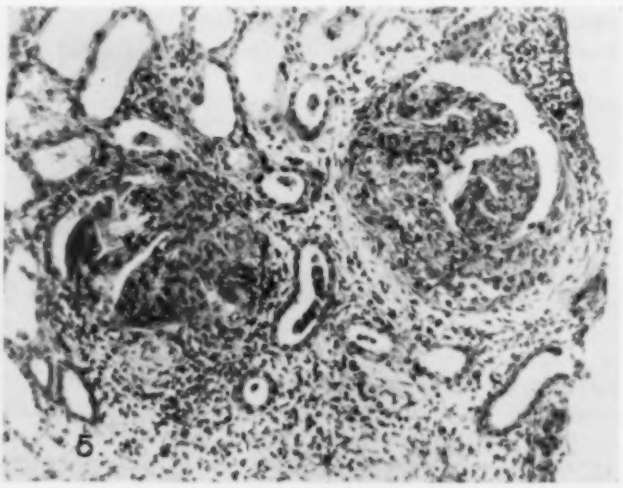


Fig. 5.—Two subcapsular glomeruli are shown to illustrate the extreme hypercellularity, crescent formation, and lack of open capillaries noted in most of the glomeruli studied in a child with disseminated lupus erythematosus (Case 1, Table 3). Hematoxylin and eosin stain; × 200.

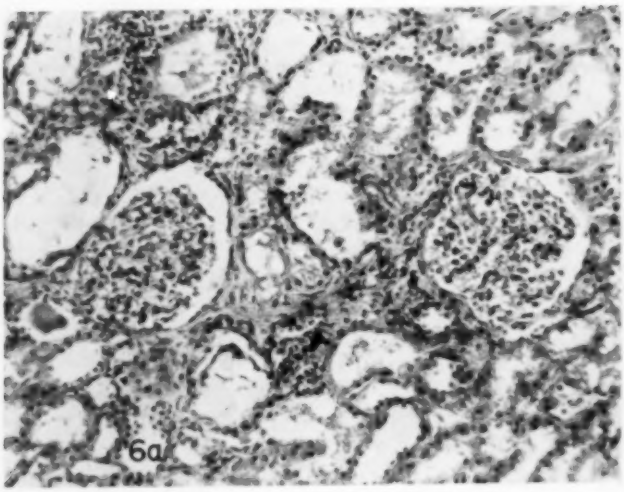


Fig. 6a.—Typical hypercellular glomeruli noted in the first biopsy specimen obtained from a child with disseminated lupus erythematosus (Case 2, Table 3). A moderate degree of tubular dilatation is also shown. Hematoxylin and eosin stain; ×110.

Discrete renal-function studies at this time were normal.

Needle biopsy of the kidney was performed four months after the onset of her illness. The glomeruli microscopically were uniformly enlarged, hypercellular, and relatively bloodless. Occasional fibrinoid thrombi were observed in the glomerular capillaries. The tubules appeared to be normal (Fig. 6a).

The patient remained in clinical remission over the next six months. The second kidney biopsy, obtained in July, 1956, revealed relatively normal glomeruli. The glomeruli were much less cellular, and, although an occasional hyaline capillary thrombus was present, these were fewer in number than were observed in the first biopsy (Fig. 6b).

The clinical remission continued for an additional year. Two additional renal biopsies confirm the evidence of improvement of the renal pathology indicated by the second biopsy.

CASE 5.—A girl's illness began in October, 1952, when she was 9 years old; at that time she developed intermittent recurrent migratory pain and swelling of the joints of the lower extremities. She was thought to have acute rheumatic fever. In April, 1953, an erythematous rash appeared over the cheeks. In July, 1953, she developed swelling and a bluish discoloration of the left leg. A diagnosis of thrombophlebitis of the left femoral vein was established. Additional physical findings noted during this illness included slight hypertension and a persistent slight fever. Laboratory

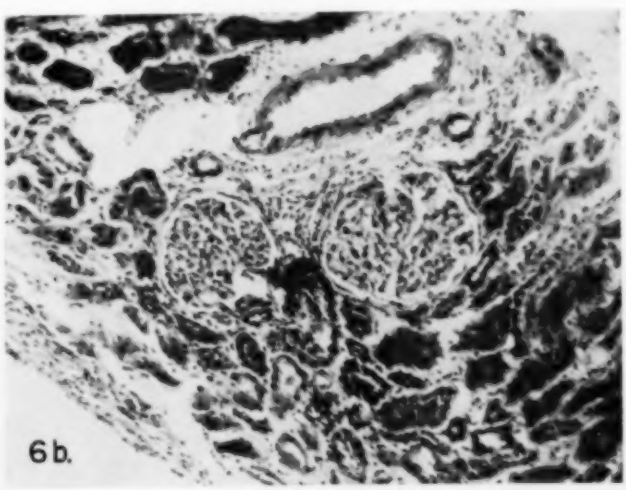


Fig. 6b.—Relatively normal glomeruli found in a biopsy specimen obtained six months after the first. Hematoxylin and eosin stain; ×110.

studies revealed albuminuria, microscopic hematuria, abnormal partitioning of the serum proteins, an atypical Wassermann reaction, signs of hepatic dysfunction, leukopenia, elevation of the erythrocyte sedimentation rate, and electrocardiographic evidence of myocarditis. A diagnosis of disseminated lupus erythematosus was considered, but numerous attempts to demonstrate the L. E.-cell phenomenon were unsuccessful.

In August, 1953, she developed manifestations of chorea. In September, 1953, she was hospitalized at the University of Minnesota for treatment of fever, stiffness of multiple joints, and swelling of the left side of the neck. On physical examination the left sternocleidomastoid muscle was noted to be swollen and tender. Distended venous channels were noted over the upper left thigh and abdomen.

The laboratory studies were similar to those recorded in July, 1953. Repeated attempts to find L. E. cells were unsuccessful. Biopsy of the swollen sternocleidomastoid muscle revealed only edematous muscle.

She developed the typical findings of acute appendicitis, but surgical exploration revealed a normal appendix. Muscle and lymph node biopsy specimens obtained at the time of the appendectomy were normal. Gradual improvement occurred, and the patient was discharged. Persistent albuminuria and microscopic hematuria were noted over the subsequent three years, although the patient was otherwise well.

She was reevaluated in March, 1957, at which time the physical examination was normal, except for an erythematous papular rash over the cheeks. Laboratory studies revealed a blood urea nitrogen of 21 mg. %, albuminuria (2.0 gm. in 12 hours), microscopic hematuria, cylindruria, and elevation of the erythrocyte sedimentation rate. Again L. E. cells were absent from preparations of the peripheral blood and the bone marrow.

A kidney biopsy revealed glomeruli in which frequent segmental areas of capillary occlusion by fibrinoid material and wire loop capillaries were noted (Fig. 7).

Comment

Renal biopsy specimens obtained from five children with disseminated lupus erythematosus have been studied to clarify the pathologic picture of the renal manifestations of this disease and in order to evaluate the effects of adrenal steroid therapy on the morphology of the renal abnormalities.

The predominant glomerular abnormality observed by light microscopy was proliferation of the endothelial cells. A spectrum of pathologic changes ranging from minimal proliferative glomerulitis to severe proliferative glomerulonephritis was noted in the several renal biopsy specimens. The degree of proliferative change observed appears to be a function of the duration and severity of the renal disease of disseminated lupus erythematosus.

The second commonest abnormality noted was focal occlusion of the glomerular capillaries by hyaline fibrinoid material. This material was more abundant in specimens which were obtained when the disease process had been active for a relatively short period clinically.

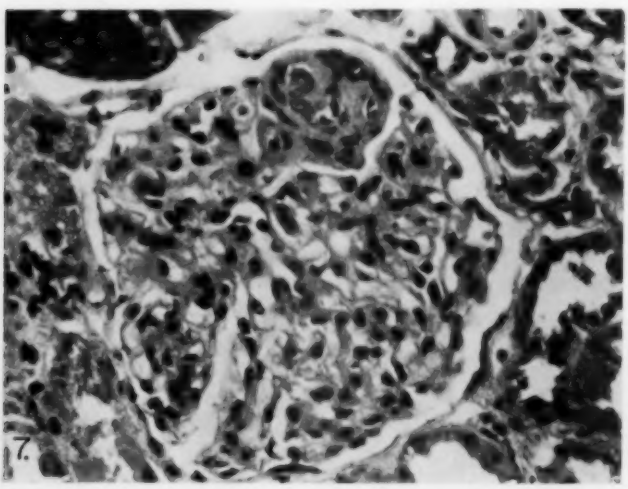


Fig. 7. — Focal hyaline lesion and basement membrane thickening in a glomerulus from a child with disseminated lupus erythematosus (Case 5, Table 3). Hematoxylin and eosin stain; × 450.

The wire-loop lesion, considered to be the characteristic morphologic renal change in disseminated lupus erythematosus, was observed in only 2 of the 11 renal biopsy specimens from this series of patients. In accordance with the findings of Muehrcke et al.,[25] it appears that this lesion is not an essential feature of the early renal change in disseminated lupus erythematosus and that the absence of this lesion should not be considered as evidence against the diagnosis of disseminated lupus erythematosus if clinical data support this diagnosis. Nevertheless, the wire-loop lesion does occur in children with disseminated lupus erythematosus after the disease has been present for a prolonged period. If present, the wire-loop change may be considered a diagnostic criterion of D. L. E., even if other laboratory manifestations are lacking.

The morphologic changes observed in the 11 renal biopsy specimens from these five children suggest the following pathogenesis of the disease: The early deposition of fibrinoid material in the renal glomerular capillaries is followed by a proliferative response of the glomerular capillary endothelial cells. The later lesion of D. L. E. may thus be indistinguishable from the glomerulitis of a variety of diseases. The effect of steroids on the early renal lesion of D. L. E. is probably related to the alterations in fibrinoid deposition which these drugs may produce. Little or no effect on the more advanced renal lesion would be anticipated. However, since the glomeruli are variably involved in the disease process, these hormones might in some cases be expected to alter the rate of destruction of the renal parenchyma.

Although the adrenal steroids have not been shown previously to alter significantly the clinical or pathologic renal manifestations of disseminated lupus erythematosus, the serial kidney biopsy specimens obtained in Cases 2, 3, and 4 suggest that the changes of proliferative glomerulitis and glomerular hyaline capillary thrombosis may be reversible. The improvement observed in the serial biopsy specimens in these three patients correlates with the clinical findings of remission and improvement of the urinary abnormalities in conjunction with steroid therapy. These data suggest that more effective methods of therapy may be developed which will result in improvement and perhaps reversal in both the clinical and the pathologic manifestations of the renal disease of disseminated lupus erythematosus.

Glomerulonephritis

Controversy over the classification of this disease has existed since the time of the original description by Bright. Thomas Addis has said, "every student of Bright's Disease constructs his own classification to meet his own interests and needs."[26] The classification includes acute, subacute, and chronic forms.

Acute glomerulonephritis is of sudden onset and is characterized by hematuria, proteinuria, oliguria, edema, and hypertension. Considerable bacteriological, epidemiological, and immunologic evidence indicates that one form of this disease is etiologically related to β-hemolytic streptococcal infection.[27,28] The titers of type-specific bactericidal antistreptococcal antibodies, which became elevated soon after the onset of the disease, may remain elevated for prolonged periods after evidence of streptococcal infection and acute glomerulonephritis has subsided.[29,30]

Chronic glomerulonephritis, of insidious onset, is characterized by the appearance of headache, edema, fatigability, and the findings of proteinuria and microscopic hematuria on routine urinalysis.

A majority of children with the subacute or chronic forms of this disease do not have a clinical history suggesting a preceding acute attack. Likewise, evidence of recurrent streptococcal infections, or significant elevation of the antistreptococcal antibody titers, is lacking in these cases.[31]

These data have led many investigators, particularly pediatricians, to regard acute

hemorrhagic glomerulonephritis, which follows streptococcal infection, as a separate disease entity. It is believed by this group that once recovery begins it is complete and that residual or progressive renal disease does not occur.[32,33]

Other workers, particularly internists and pathologists, view acute glomerulonephritis as a reflection of one phase of a disease process, which may terminate in chronic glomerulonephritis with insufficient, contracted kidneys.[24,34,35] To this view, streptococcal infection is only one of several possible etiologic factors in the development of the disease, and some series have been reported in which progressive chronic renal disease is considered to have developed from as many as 50% of the acute cases.[35] Contributing to the confusion is the fact that exacerbation of latent and chronic glomerulonephritis may simulate acute nephritis clinically. It seems likely that some patients with renal disease diagnosed as acute glomerulonephritis have in fact exacerbations of subacute or chronic glomerulonephritis. Furthermore, on occasion, patients with underlying chronic renal disease may have superimposed acute glomerulonephritis. These possible combinations make the outcome of acute glomerulonephritis in a given patient difficult to assess on clinical grounds alone.

Several morphologic classifications of glomerulonephritis have been proposed. Although a histologic classification would appear to offer a rational basis for differentiation of the various syndromes, it is often impossible to reconcile the clinical course of an individual patient with the structural abnormalities observed in the kidney.

Bell [24] has proposed that glomerulonephritis proceeds from the acute proliferative stage to (1) recovery, (2) active subacute glomerulonephritis, or (3) latent chronic glomerulonephritis. The exact mechanism of progression of acute glomerulonephritis to the subacute or chronic forms is not clearly understood. Variations in the basic patterns of alteration are observed frequently, and the rate of progression varies greatly from case to case. Unfortunately, the pathologist studying postmortem material must often attempt to construct the natural history of an illness by studying its end-stage, while material available to estab-

TABLE 4.—*Renal Biopsy in Glomerulonephritis*

Case	Clinical Diagnosis	Duration of Disease at Biopsy	Age, Yr.	Clinical Laboratory Data *				Pathologic Diagnosis of Glomerulonephritis	Subsequent Course
				Hypertension	Alb. & RBC	Reduced Function	ASO Titer		
1	Acute glomerulonephritis	1 mo.	6	—	+	+	720	Acute	Well 2 yr.
2	Acute glomerulonephritis	1 mo.	3	+	+	+	1,275	Acute	Well 1½ yr.
3	Acute glomerulonephritis	2 wk.	11	+	+	+	877	Acute exacerbation of chronic	Chronic renal disease
4	Acute glomerulonephritis	3 wk.	4	+	+	—	230	Acute	Well 6 mo.
5	Acute glomerulonephritis Subacute glomerulonephritis	2 wk. 1 yr.	13	+ —	+ +	Anuria +	166 250	Subacute Chronic	Chronic renal disease
6	Subacute glomerulonephritis	6 mo.	12	+	+	—	50	Subacute	Chronic renal disease
7	Subacute glomerulonephritis	7 mo.	14	—	+	—	50	Subacute	Chronic renal disease
8	Chronic glomerulonephritis	3 yr.	8	+	+	+	50	Chronic	Died
9	Chronic glomerulonephritis	5 mo.	13	+	+	+	50	Chronic	Died
10	Chronic glomerulonephritis	3½ yr.	9	—	+	—	50	Chronic	Chronic renal disease
11	Chronic glomerulonephritis	1½ yr.	14	+	+	+	100	Chronic	Chronic renal disease
12	Chronic glomerulonephritis	2 yr.	15	+	+	+	125	Chronic	Chronic renal disease
13	Chronic glomerulonephritis	6 yr.	16	+	+	+	100	Chronic	Chronic renal disease
14	Chronic glomerulonephritis	2 yr.	15	+	+	+	50	Chronic	Chronic renal disease

* +, present; —, absent; ASO titer, antistreptolysin O antibody titer in Todd units per millimeter; Alb., urinary protien; RBC, hematuria; reduced function, evidence of decreased renal function.

lish the intermediate stages is often inadequate. It is in this regard that serial renal biopsies may prove of greatest value, namely, in filling gaps in existing knowledge and establishing the natural histories of acute and chronic nephritis.

The present material includes clinical, physiologic, and pathologic data obtained from renal biopsy in 14 cases of glomerulonephritis (Table 4). In four cases the clinical course and association of the disease with evidence of recent streptococcal infection is in keeping with the clinical diagnosis of acute hemorrhagic glomerulonephritis. The pathologic changes, as determined by renal biopsy, are compatible with the accepted lesion of acute glomerulonephritis. Three of these children have made uneventful and apparently complete recoveries. The fourth has continuing renal disease and will be described in detail.

Three cases of clinical subacute or latent chronic glomerulonephritis and seven cases of clinical chronic glomerulonephritis are included.

Case Reports—Glomerulonephritis

CASE 2.—*Acute glomerulonephritis*

A 3 ¼-year-old boy developed an upper respiratory infection characterized by fever, rhinitis, and cough in early January, 1956. He was treated with a single injection of penicillin. On Jan. 14, 1956, his urine was noted to be reddish brown.

On admission to the hospital, two days later, he was found to have a slight fever and mild hypertension (117/90). Laboratory study revealed albuminuria, hematuria, and pyuria; elevation of the blood urea nitrogen (69 mg. %, and elevation of the erythrocyte sedimentation rate (ESR) to 112 mm. in an hour. A throat culture grew β-hemolytic streptococci. An antistreptolysin O (ASO) titer obtained upon admission was 1275 units per cubic centimeter. An x-ray of the chest revealed bronchopneumonia.

The patient improved rapidly over the subsequent month, with a gradual return of the blood urea nitrogen to normal. At the time of the kidney biopsy, on Feb. 17, 1957, moderate elevation of the erythrocyte sedimentation rate and moderate microscopic hematuria were the principal abnormal laboratory findings.

Microscopic examination of the kidney biopsy specimen revealed moderately enlarged hypercellular glomeruli. The capillary lumina were narrowed by proliferation of the endothelial cells, and the glomeruli appeared relatively ischemic (Fig. 8).

The patient has been followed for 18 months and appears to have completely recovered, in that an Addis count of a recent 12-hour urine specimen was normal.

CASE 3.—An 11-year-old white boy was noted to fatigue easily, complained of severe headache, and developed generalized edema one week before admission. Ten days earlier he had complained of a sore throat, and swollen tender submandibular lymph nodes and a low-grade fever was noted, but no antibiotic therapy was given. Although he had had several bouts of sore throats each winter, no previous renal symptomatology had been observed.

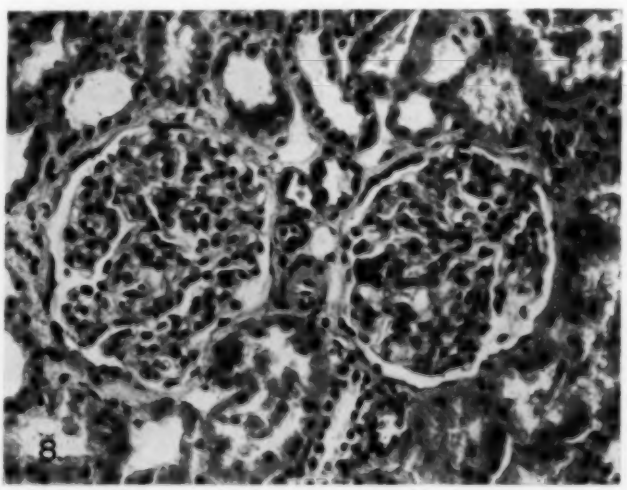


Fig. 8. — Two enlarged hypercellular glomeruli from a child with acute glomerulonephritis (Case 2, Table 4). There are few open capillaries. Hematoxylin and eosin stain; ×150.

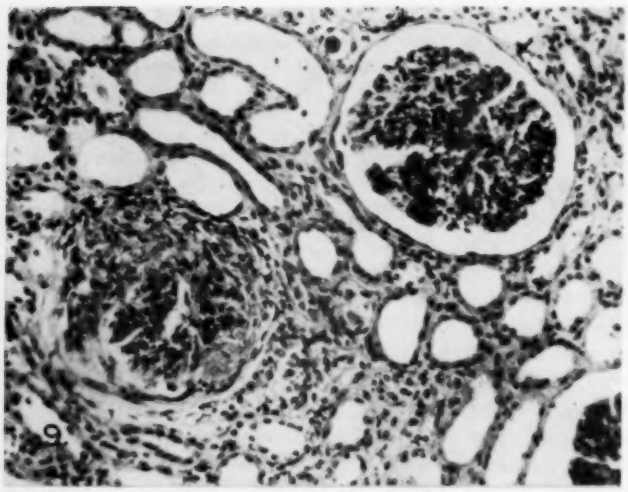


Fig. 9. — Renal biopsy specimen from a child who developed an acute exacerbation of chronic glomerulonephritis after streptococcal infection (Case 3, Table 4). The upper right glomerulus illustrates the acute proliferative reaction with numerous polymorphonuclear leukocytes. The lower left glomerulus is fibrotic and contains a large crescent. Moderate tubular atrophy is shown. Hematoxylin and eosin stain; × 150.

The physical examination on admission revealed an apprehensive lethargic boy. An erythematous maculopapular rash was present over the upper extremities and back. His blood pressure was 156/110 mm. Hg. Minimal pharyngeal injection, periorbital edema, and 2+ edema of the lower extremities were noted. The significant laboratory abnormalities included 2+ albuminuria, 2+ to 3+ red blood cells, and occasional red blood cell casts on urinalysis. The ESR was 90 mm. in an hour. The BUN was 90 mg. %. A throat culture revealed numerous β-hemolytic streptococci which were later shown to be Type 12. The ASO titer was 877 units two weeks after the acute illness.

Renal biopsy was first performed approximately two weeks after the onset of the first symptoms of renal disease. Study of the microscopic sections of the tissue revealed two types of pathology, one acute and the second chronic.

The acute lesion consisted of diffuse glomerular enlargement, severe polymorphonuclear infiltration of the glomeruli, striking endothelial-cell proliferation, and glomerular ischemia. The second lesion was characterized by glomerular fibrosis with epithelial-cell crescent formation and moderate tubular atrophy (Fig. 9).

A second biopsy was performed one month after the first, at which time the patient was clinically improved. Definite regression of the acute glomerular changes observed in the first biopsy specimen was apparent, but there was no change in the chronic glomerular pathology.

The patient's renal function improved but was not normal. Routine urinalysis continued to reveal albuminuria and hematuria. The ESR was 65 mm. in an hour.

This patient has been followed in the outpatient department for 18 months since the acute attack of nephritis. Recent routine urinalyses have been normal, but Addis counts of 12-hour urine specimens continue to reveal significant albuminuria and hematuria. He is clinically well and attends school regularly.

We believe that this case represents an example of a child suffering from latent chronic glomerulonephritis in whom infection with Type 12 streptococci produced an exacerbation of acute hemorrhagic nephritis.

Case 5.—A 13-year-old white girl was referred to the pediatrics-urology service of the University of Minnesota Hospitals on May 3, 1955, for treatment of acute anuria of four days' duration. She had been perfectly well until April 23, 1954, when she complained of back pain during a mild upper respiratory infection. Sudden severe anuria necessitated her admission to another hospital, where a complete urologic examination failed to reveal a cause for the anuria. Only a few milliliters of urine was obtained during the four days she was studied at that hospital. She was referred to the university hospital when clinical and laboratory evidence of uremia was noted to be increasing rapidly.

Physical examination on admission revealed an acutely ill, slightly edematous child. She vomited frequently. Her blood pressure was 120/80 mm. Hg. There were no other significant physical abnormalities.

The results of initial laboratory studies included BUN of 212 mg. %, serum chloride of 76 mEq. per liter, serum sodium of 122 mEq. per liter, and serum potassium of 8.1 mEq. per liter. The ESR was 122 mm. in an hour. A throat culture grew no pathogens. The serum ASO titer was 166 Todd units per milliliter. The few milliliters of urine which was obtained on catheterization of the

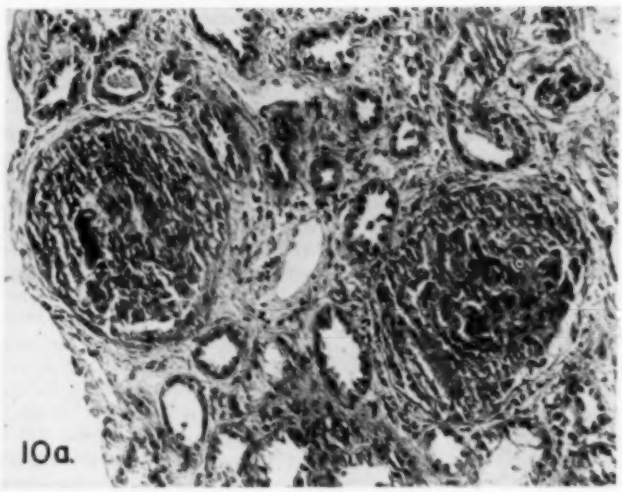


Fig. 10a.—Two glomeruli from a child with anuria (Case 5, Table 4). The uniformly severe proliferative reaction and striking crescent formation are compatible with a pathological diagnosis of subacute glomerulonephritis. All 14 of the glomeruli in the biopsy specimen showed maximal proliferation. Hematoxylin and eosin stain; × 200.

bladder was grossly bloody and contained 4+ albumin.

An attempt at extracorporeal dialysis by use of the artificial kidney on May 4, 1955, was considered unsatisfactory because of poor blood flow. The patient was managed by frequent peritoneal dialyses over the subsequent 13 days. Clinical peritonitis, which developed on May 18, 1955, forced the discontinuation of this method. A renal biopsy specimen was obtained on May 16, 1955, and the tissue was studied microscopically with a number of staining techniques. Each of the 12 glomeruli obtained revealed severe endothelial proliferation and extensive epithelial crescent formation. The pathologic diagnosis was subacute glomerulonephritis (Fig. 10a).

In the hope that the renal lesion might be altered by adrenocortical therapy, this patient was given large doses of hydrocortisone intravenously, beginning on May 21, 1955. There was a progressive increase in the urine volume from May 23 forward. A urine volume of 1000 cc. per day was obtained on May 28. The patient improved progressively thereafter. Although her BUN was normal by June 23, there was evidence of severe renal functional impairment by clearance techniques. Routine urinalysis revealed 1+ albuminuria and occasional RBC.

A second renal biopsy specimen was obtained on July 11, but, unfortunately, no glomeruli were found in this specimen. The tubules were noted

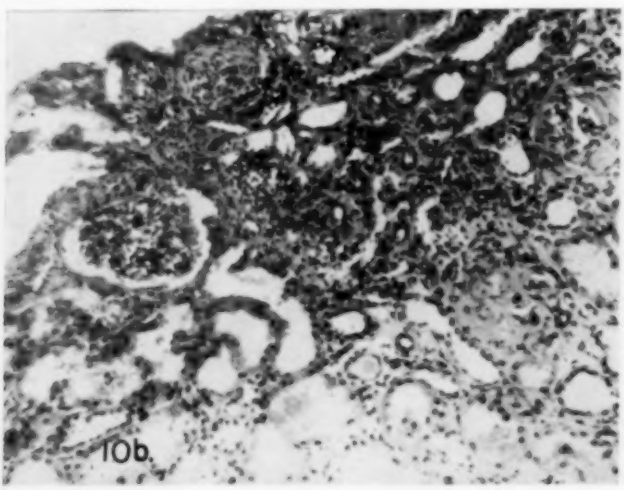


Fig. 10b.—A second biopsy specimen, one year later, revealed fibrosis of the majority of glomeruli. A few glomeruli appeared to be improved in comparison with the earlier specimen. Tubular atrophy and dilatation are evident. Both progression to fibrosis and improvement were noted in the glomeruli of the second biopsy specimen. Hematoxylin and eosin stain; × 110.

to be slightly dilated, and an occasional granular cast was observed.

The patient was discharged on July 13 and was followed closely by her local physician. She continued to receive large doses of hydrocortisone orally for nearly one year, since attempts to withdraw the drug were associated with an increase in albuminuria and a sharp rise in the ESR. She was at this time clinically well and moderately active, and she continued to attend school. Her blood pressure was normal. Severe Cushingoid changes have been present since shortly after the onset of the steroid therapy.

She was readmitted on April 15, 1956, one year after the onset of her disease. At that time the patient was receiving small doses of hydrocortisone. Her renal function was found to be about 60% of normal by clearance methods. Urinalyses and Addis counts of 12-hour specimens revealed moderate albuminuria and an increased number of red blood cells and casts. The ESR was 43 mm. in an hour. An intravenous pyelogram was normal. A third renal biopsy specimen was obtained at that time.

The microscopic renal morphology was characterized by marked glomerular hyalinization and fibrosis. An occasional epithelial-cell crescent, similar to the principal lesion of the first biopsy specimen, was again noted. An occasional glomerulus revealed only segmental areas of capillary fibrosis, the remaining capillaries retaining a relatively normal appearance. There was moderate interstitial cellular reaction and moderate tubular atrophy (Fig. 10b). We interpret these observations to demonstrate that both progressive destruction and healing may occur among glomeruli extensively involved in the diffuse proliferative process characteristic of subacute glomerulonephritis.

Case 11.—An 11-year-old girl was noted to have periorbital edema in October, 1953. No significant pharyngitis had occurred in the few months preceding this symptom. Her parents could not recall symptoms at any time which might have resembled acute glomerulonephritis. Physical examination at that time revealed periorbital and slight pretibial edema and moderate hypertension.

She was studied at the University Hospitals in July, 1954. Her blood pressure was 140/110 mm. Hg. Laboratory findings included 33,000,000 red blood cells, 15,000,000 white blood cells, and 1.2 gm. protein in a 12-hour urine specimen; blood urea nitrogen was 16 mg. %; erythrocyte sedimentation rate, 80 mm. in an hour; serum albumin, 2.1 gm. %; serum globulin, 3.1 gm. %, and serum cholesterol, 230 mg. %. Renal clearance studies revealed inulin clearance to be 77 cc. per minute and *p*-aminohippurate clearance, 567 cc. per minute. Intravenous and retrograde pyelograms were normal. The serum ASO titer was 125 units per milliliter.

The patient was treated with antihypertensive drugs, with a satisfactory response in blood pressure.

The physical findings and laboratory studies which were completed prior to a surgical kidney biopsy performed in May, 1955, were similar to those listed above.

Microscopic study of the renal tissue revealed severe fibrosis and lobulation of most of the glomeruli. Periodic acid-Schiff stains showed numerous masses of fibrinoid material between and within the capillary loops. The pathologic diagnosis was chronic glomerulonephritis (Fig. 11).

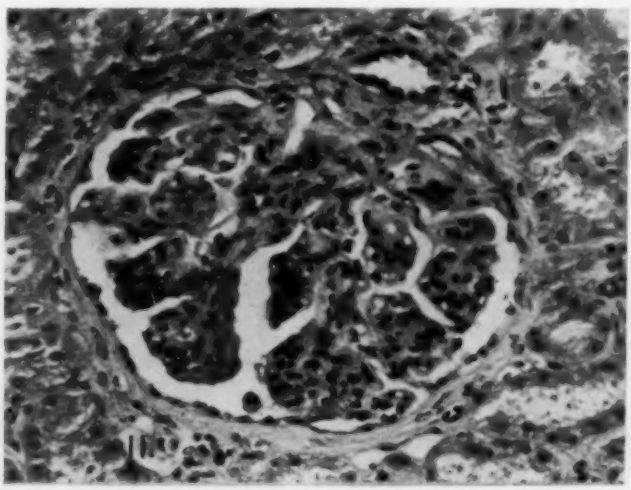


Fig. 11.—Striking lobulation, basement membrane thickening, and fibrosis of a typical glomerulus from a child with chronic glomerulopenhritis (Case 11, Table 4). Bowman's capsule is also thickened. Hematoxylin and eosin stain; ×450.

The laboratory and physical findings have not changed appreciably in the two and one-half years the child has been followed since the kidney biopsy.

Comment

The clinical and pathologic features of 14 cases of glomerulonephritis in children have been presented. The morphologic changes observed by renal biopsy in these children may be classified in keeping with the current accepted nomenclature as acute glomerulonephritis, subacute glomerulonephritis, and chronic glomerulonephritis. However, considerable difficulty was encountered when an attempt was made to correlate the clinical features of the disease with the pathologic diagnosis as determined by kidney biopsy. Further, it was impossible in some instances to predict the severity of the renal lesion in clinical subacute or latent chronic glomerulonephritis by renal-function tests or other laboratory data. Renal function, as determined by clearance of inulin, *p*-aminohippurate, urea, or creatinine, was normal except in very severe glomerular disease.[36] This observation suggests that the current methods for measurement of renal function are relatively insensitive and that severe morphologic renal changes may be present in the absence of significant limitation in glomerular filtration rate or effective renal plasma flow. This observation does not detract from the value of serial renal-function studies used in following the progress of a renal disease in an individual patient.

The pathologic alterations noted in acute (streptococcal) glomerulonephritis are distinctive when the clinical diagnosis of acute glomerulonephritis is limited to include only those patients in whom a preceding streptococcal infection (proved by bacteriologic or by immunologic methods) is followed by glomerulonephritis of acute onset in a patient without preexisting renal disease. An exception to this concept is illustrated by Case 3, which we believe represents an acute post-streptococcal nephritis superimposed upon underlying, previously undiagnosed, latent chronic glomerulonephritis.[31] This case illustrates the value of renal biopsy in the study of the pathogenesis of glomerulonephritis and supports the concept that in some instances in which clinical acute glomerulonephritis has been reported to progress to chronic renal disease the acute episode may have occurred in a patient with preexisting, clinically unrecognized, subacute or chronic glomerulonephritis. The simultaneous occurrence of two distinct clinical and pathologic entities may well explain certain discrepancies which exist in the literature relative to the prognosis of acute glomerulonephritis.

Further information pertaining to the pathogenesis of subacute glomerulonephritis and the progression of the disease to typical chronic glomerulonephritis is provided by study of Case 5. In this child, acute anuria was associated with the pathologic renal lesion described as subacute glomerulonephritis. Striking clinical improvement and return of renal function occurred, and the child continued her activities in relatively good health for an interval of about 10 months. One year after the original illness, a third kidney biopsy revealed the typical pathologic alterations of chronic glomerulonephritis. In the interval between the first and last kidney biopsy many glomeruli had undergone hyalinization and fibrosis and were functionally removed from the circulation. These findings would be in keeping with the accepted concept that subacute proliferative lesions can progress to scarring and hyalinization. It seems especially important to note, however, that a small percentage of glomeruli in the last biopsy specimen were normal. This finding suggests that the dramatic physiological improvement in this patient stems from healing of the proliferative pathology noted in all the glomeruli in the first biopsy specimen. The observation of relatively normal glomeruli in the last biopsy specimen indicates either that some of the severely deformed crescentric glomeruli of the first biopsy specimen (all 13 glomeruli visualized were similarly involved) had been repaired and had reverted to the normal histologic

pattern or that the initial biopsy specimen was not representative of the kidney pathology at that time. We favor the former hypothesis, since our experience with kidney biopsy in diffuse renal disease thus far indicates that a sample of 10 or more glomeruli provides representative pathology of the renal architecture in a given kidney. Further, the complete anuria which this child manifested would make it seem unlikely that functionally normal glomeruli were present during the subacute attack.

Although it is not wise to draw broad generalizations from a single case, these observations suggest that, at a certain stage, the lesions of subacute glomerulonephritis, in addition to being progressive, may at the same time be at least partly reversible. This view makes efforts to induce reversal of even severe renal glomerular lesions seem more holpeful. The role of hydrocortisone in influencing the improvement noted in this case is not clear. A search for other agents or methods of therapy in this disease must continue.

The cases of chronic glomerulonephritis in this series include (1) those of insidious onset, (2) those with typical latent chronic clinical symptomatology, and (3) a case of insidious onset with rapidly fatal termination. No significant differences in the microscopic pathology in these various forms of chronic glomerulonephritis were detected.

It would seem that incisive information concerning the pathogenesis of this group of diseases is needed and that this knowledge may well be acquired through the analysis of serial kidney biopsy specimens in patients with glomerulonephritis. Such observations can then be correlated with critical physiologic, biochemical, bacteriologic, immunologic, and histochemical investigations in these same patients.

The Nephrotic Syndrome

The nephrotic syndrome is characterized clinically by edema, proteinuria, hypoproteinemia, hypoalbuminemia, and hyperlipemia. This complex of symptoms is known to occur in association with certain recognized systemic diseases, such as amyloidosis, diabetes mellitus, lupus erythematosus, syphilis, and malaria. The nephrotic syndrome may also develop as a consequence of renal vein thrombosis, following drug toxicity (viz., trimethadione [Tridione] and gold and mercury salts), and after bee stings or poison oak dermatitis. The great majority of cases of the nephrotic syndrome in childhood, however, develop in the absence of any known toxic agents and are unrelated to other systemic illnesses.

The relationship of the nephrotic syndrome to other forms of chronic renal disease is widely disputed among clinicians and pathologists. Three divergent views are held and have been summarized by Barnett et al.[37] as follows:

1. The nephrotic syndrome is in all cases a stage of chronic glomerulonephritis in which the onset of acute glomerulonephritis occurred weeks, months, or years before but was not recognized.

2. The nephrotic syndrome occurs as two distinct diseases. The first, pure, or lipoid, nephrosis, is unrelated to glomerulonephritis and (*a*) manifests minimal, if any, nephritis clinically and (*b*) is associated with complete recovery in a majority of cases. The second disease is regularly associated with glomerulonephritis and is either a stage of chronic nephritis or a distinct disease (chronic nonspecific nephritis or nephrotic nephritis).

3. The nephrotic syndrome is a distinct disease entity which is not related to acute or chronic glomerulonephritis of other types but in which persistent hematuria, hypertension, or reduction in renal function may occur.

This latter view appears to provide the best working definition of the nephrotic syndrome in children, in our experience.

The nephrotic syndrome is commonest between the ages of 1 and 4 years. In a typical case, a previously healthy child is noted to develop periorbital edema in the absence of other abnormalities. About one-half of the cases give a history of a non-

specific upper respiratory infection prior to the onset of edema, but no characteristic bacterial or viral agent has been demonstrated as an important etiologic agent. The edema increases to massive anascarca in many instances. The characteristic laboratory findings of proteinuria, hypoalbuminemia, and hypercholesteremia, which are essential to the diagnosis, are present in varying degrees throughout the active period of the disease.

The prognosis in any given child is based upon statistical data alone, since there is no reliable clinical guide which will foretell the outcome in early cases. Hypertension and hematuria are generally regarded as poor prognostic signs; yet recovery has been observed in many instances where both of these findings were prominent. Heymann and his associates [38] have recently proposed that hyperglobulinuria is a poor prognostic sign. A good response to initial therapy does not always appear to be a reliable indication of a favorable outcome.[39,40] Numerous attempts to correlate the eventual outcome with the renal function of a given case have been disappointing.[41]

Now that it is possible to control infection in these children, it is believed that about 40% to 60% of children with nephrosis ultimately recover. The relatively recent use of the pituitary-adrenocortical hormones in the treatment of nephrosis has not been critically evaluated in well-controlled studies, but most students of the disease agree that with the aid of steroid therapy as many as 70% to 80% of the cases may recover.[40,42,43] The children who do not ultimately recover usually follow a course of recurrent bouts of edema during which progressive signs of renal insufficiency and nephritis appear. At the present time most of the patients who die succumb to renal failure.

The pathology of the nephrotic syndrome has been a subject of controversy since Volhard and Fahr,[44] in 1914, first described nephrosis as an entity distinct from other forms of Bright's disease.

The occurrence of hyaline and fatty droplets in the cells of the proximal tubules was once considered to be the primary pathologic change in nephrosis. Bell [24] directed attention to the glomerular changes and suggested that the tubular changes were secondary to resorption of protein and lipid materials. Study of the basement membranes of the glomerular capillaries with special stains by other investigators [45] has confirmed the work of Bell, and it is now generally agreed that diffuse thickening of the basement membrane is the most characteristic pathologic alteration in nephrosis. However, glomerular lesions are not uniformly demonstrable in the kidneys of patients with nephrosis. At least 50 cases have been collected by Rytand [46] in which no glomerular lesions could be demonstrated with any staining technique by light microscopy.

The histologic renal glomerular abnormalities found at autopsy in patients who develop the nephrotic syndrome associated with chronic glomerulonephritis are readily recognizable and are indistinguishable from the changes characteristic of chronic glomerulonephritis without the nephrotic syndrome.

The crucial question revolves around the relationship between the pathologic entity "pure" nephrosis and the nephrotic syndrome in chronic glomerulonephritis. Would the histologic pattern of "pure" nephrosis have become transformed into that of chronic glomerulonephritis had the patient survived? Further, might the histologically normal kidney have been altered to resemble the kidney in membranous glomerulonephritis (Bell)? Which lesion is reversible and is associated with recovery? What morphologic changes occur with recovery, and what is the effect of therapy on the pathology in a given case?

In an attempt to answer some of these questions we have embarked on a broad study of the nephrotic syndrome. Included

TABLE 5.—*Renal Biopsy in the Nephrotic Syndrome*

Case	Age, Yr.	Duration at Biopsy	Pathologic Diagnosis
1	12	2 mo.	Minimal proliferative glomerulonephritis
		3 mo.	Same
		11 mo.	Same
2	5½	2 mo.	Normal
		4 mo.	Minimal proliferative glomerulonephritis
3	3	2 mo.	Normal
4	12	6 mo.	Minimal proliferative glomerulonephritis
5	3½	7 mo.	Normal
6	3	1 mo.	Minimal proliferative glomerulonephritis
7	10	2 mo.	Normal
8	12	4 mo.	Normal
9	2½	2 mo.	Normal
10	2½	2½ mo.	Normal
11	3	4 mo.	Normal
12	3½	1 mo.	Normal
13	4½	4 yr.	Normal
14	3½ mo.	3 mo.	Normal
15	5	2½ yr.	Normal
16	6	3½ yr.	Moderate proliferative glomerulonephritis
17	10½	3½ yr.	Minimal proliferative glomerulonephritis
	11	4 yr.	Minimal proliferative glomerulonephritis
18	4	1 wk.	Normal
		1 mo.	Normal
19	6½	5 yr.	Normal
20	6	4 mo.	Moderate proliferative glomerulonephritis
21	8 mo.	1 mo.	Minimal proliferative glomerulonephritis
Mixed nephrosis-nephritis			
22	8 mo.	2 mo.	Lobular glomerulonephritis
23	3	1½ yr.	Lobular and membranous glomerulonephritis
24	1¼	1 yr.	Subacute glomerulonephritis
		2½ yr.	Membranous glomerulonephritis
25	15	2½ yr.	Lobular glomerulonephritis
26	10	3½ yr.	Lobular glomerulonephritis
27	7½	7 yr.	Lobular & membranous glomerulonephritis
28	12	3 yr.	Lobular glomerulonephritis
Nephrosis in remission			
29	7	3 yr.	Normal
30	7	10 mo.	Normal
31	6	2 yr.	Minimal proliferative glomerulonephritis

in the clinical study are patients with nephrosis associated with unusual circumstances which we have looked upon as possible "experiments of nature."[47] Special efforts are being made to clarify the significance of the nephrotic syndrome occurring (1) as a result of bee stings, (2) as a familial disease,[48,49] (3) in very young infants, (4) as an "epidemic" disease, and (5) as a result of drug intoxication or sensitivity.

Rytand[50] has reported the occurrence of nephrosis as a reaction to bee sting. We have studied four children in whom the nephrotic syndrome followed a bee sting. Two of these cases have been studied by renal biopsy and are included in the present report as examples of the nephrotic syndrome in chronic glomerulonephritis (Cases 23 and 26, Table 5). Further study of the possible role of bee venom in the etiology of nephrosis is in progress.

The nephrotic syndrome rarely occurs before one year of age. However, we have recently studied eight children in whom nephrosis had its onset before the age of 6 months. One of these cases is included in this report (Case 22, Table 5). The significance of the occurrence of the nephrotic syndrome in the very young child is not known, but further study of this "experiment of nature" may well provide important information relating to the etiology and pathogenesis of this disease.

In the course of our investigation of the nephrotic syndrome, we have recently discovered that seven children with nephrosis live in a small (pop. 20,000) southwestern Minnesota community. The crude incidence of the disease in this community (35 per 100,000) contrasts sharply with the reported incidence of nephrosis in children (3 per 100,000) in the population at large.[51] Preliminary study of these children has failed to reveal any characteristic clinical features which distinguish nephrosis in the "epidemic" form from the nephrotic syndrome as it usually occurs. Further study

of these children, including renal biopsy, is in progress.

We have obtained 37 satisfactory renal biopsy specimens in 31 cases of nephrosis in childhood, including clinical cases of "pure" nephrosis, so-called "mixed" nephrosis-nephritis, and the nephrotic syndrome in chronic glomerulonephritis. Four patients have been studied in remission after apparent recovery from nephrosis (Table 5).

None of the patients has a history of renal disease preceding the onset of the nephrotic syndrome. The cases which have been classified for this study as clinically "pure" have, after extensive study, failed to reveal evidence of nephritis. Those cases classified as mixed nephrosis-nephritis are patients in whom hematuria, mild hypertension, or minimally reduced renal function were noted. The diagnosis of the nephrotic syndrome with chronic glomerulonephritis is used to designate those patients in whom persistent hematuria, constant hypertension, and some degree of renal insufficiency had been present for one year or more but in whom the initial illness was characterized by the nephrotic syndrome.

Case Reports—Nephrotic Syndrome

CASE 1 (Table 5).—A 12-year old girl noted the insidious onset of edema of her face and feet in November, 1955. Albuminuria was detected by her family physician, who suggested hospitalization at that time. There was no history of preceding infection or of preceding renal disease. The patient was admitted to the University of Minnesota Hospitals in December, 1955. The physical examination was remarkable only because of moderate edema and ascites. Her blood pressure was 118/90.

The significant results of laboratory studies included 2+ albumin in a routine urinalysis and 2.0 gm. of protein, 36,000,000 WBC, 3,200,000 RBC, and 100,000 casts in a 12-hour urine specimen. The ESR was 59 mm. in an hour; BUN, 14 mg. %; serum albumin, 1.0 gm. %; serum globulin, 2.7 gm. %; serum cholesterol, 541 mg. %; ASO titer, 50 units per milliliter. Her renal function was normal.

A renal biopsy specimen obtained on Jan. 5, 1956, revealed minimal proliferation of the endothelial cells of the glomerular capillaries. There was no evidence of significant glomerular capillary obstruction, basement membrane thickening, or glomerular fibrosis.

The patient received cortisone in large doses for 20 days. She lost 38 lb. of body weight in a diuresis which began on the 16th day of therapy. A rise in serum albumin to 3.0 gm. %, a fall in the serum cholesterol level to 239 mg. %, and the disappearance of albuminuria were observed. The ESR declined to 33 mm. an an hour but never returned to normal.

A second renal biopsy specimen was obtained on Feb. 3, one month after the first specimen and at the time of clinical remission. There was no recognizable change in the morphology of this tissue when compared with light microscopy to the first biopsy specimen.

The patient had been "well" for only two weeks when albuminuria recurred along with a rise in the ESR to 85 mm. in an hour. She was retreated with corticotropin (ACTH) in large doses for 17 days. A diuresis and marked improvement in her abnormal laboratory findings were again observed. Cortisone was given on three days of each week over the subsequent six weeks. She again became edematous and was found to have all the characteristic laboratory abnormalities of the nephrotic syndrome on May 15, 1956.

Large amounts of cortisone given for 26 days failed to alter appreciably the clinical or laboratory evidence of the disease. Two courses of mechlorethamine hydrochloride (nitrogen mustard) (0.4 mg. per kilogram of body weight in two divided doses intravenously) also failed to modify the disease significantly. A second course of corticotropin, which was given in late July, 1956, was discontinued after 10 days because of vomiting, uremia, acidosis, and hyperkalemia. All these severely abnormal chemical values subsequently returned to normal, but there was no evidence of improvement in the basic clinical and laboratory abnormalities.

The third kidney biopsy specimen was obtained on Sept. 5, 1956. A striking change in the renal morphology, as compared with that of the two earlier biopsy specimens, was now evident. Segmental glomerular fibrosis, epithelial-cell crescents, fibrinoid occlusion of glomerular capillaries, moderate interstitial round-cell infiltration, and moderate tubular atrophy and dilatation were evident. The pathologic diagnosis was early chronic glomerulonephritis.

The patient has recently had a remarkable spontaneous diuresis of 48 lb. at home. However, she continues to have intermittent edema, albuminuria, hypoalbuminemia, and hypercholesteremia. The sedimentation rate is 110 mm. in an hour (Figs. 12a and 12b).

CASE 22 (Table 5).—An 8-month-old white boy was admitted to the University of Minnesota Hos-

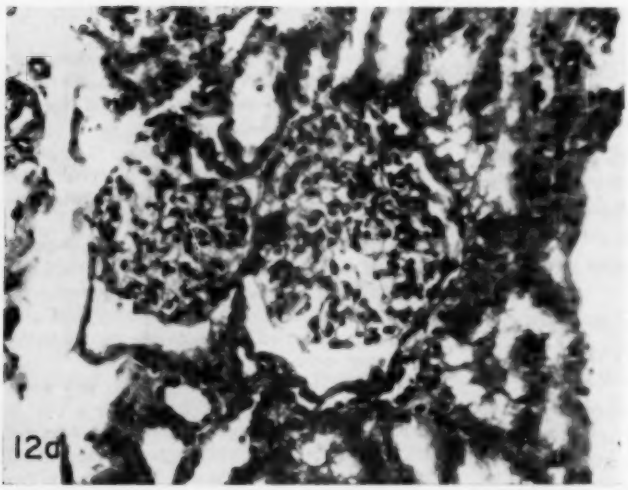


Fig. 12a.—Minimal endothelial proliferation in two glomeruli from a child with "pure" nephrosis (Case 1, Table 4). The basement membranes are not abnormal. Hematoxylin and eosin stain; × 250.

pitals on Nov. 15, 1955, three weeks after the insidious onset of ankle edema. The edema had increased progressively and had become generalized prior to admission. No previous renal disease had been suspected. The pregnancy and delivery had been normal. There was no history of renal disease in the family, and the patient's 10 siblings were well.

The physical examination on admission revealed a pale lethargic severely edematous child who appeared chronically ill. His blood pressure was moderately elevated (120 mm. Hg systolic). A mild hypospadius and bilateral cryptochidism were noted.

Laboratory Studies: A urine specimen contained 3+ albumin, very occasional casts, and occasional red blood cells. The BUN was 100 mg. %; the CO_2-combining power, 10 mEq. per liter, and the serum potassium, 6.0 mEq. per liter. The serum albumin was 0.7 gm. %; the serum globulin, 2.6 gm. %, and the serum cholesterol, 434 mg. %. Throat culture grew no pathogens, and the serum ASO titer was less than 50 Todd units.

A surgical renal biopsy specimen was obtained on Dec. 2, 1955. The microscopic examination of this tissue revealed profound diffuse glomerular alterations, consisting of marked capillary basement membrane thickening with segmentation and obliteration of the capillary bed. Occasional glomeruli were completely hyalinized. An occasional epithelial crescent was observed. Extensive tubular

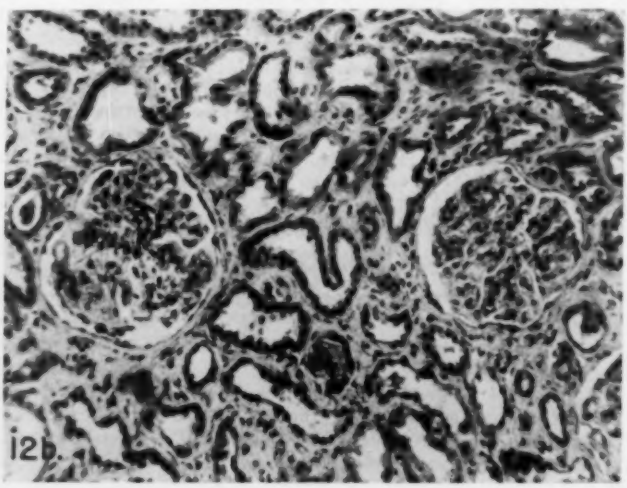


Fig. 12b.—Another renal biopsy specimen, obtained nine months after the first, shows moderate basement membrane thickening and significant glomerular fibrosis with fewer open capillaries. Hematoxylin and eosin stain; × 150.

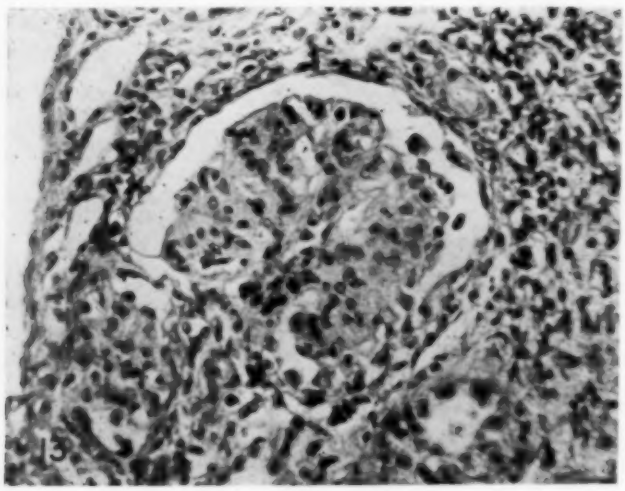


Fig. 13.—Typical glomerulus from an infant 8 months of age with clinical "mixed" nephrosis-nephritis (Case 22, Table 5). Severe fibrosis, basement membrane thickening, and occlusion of capillaries are shown. Hematoxylin and eosin stain; × 300.

atrophy, with interstitial fibrosis and reactive inflammation, was also present (Fig. 13).

The patient was treated with mechlorethamine intravenously in the hope that the disease process might be altered favorably, but no significant improvement was noted. The renal insufficiency progressed, and the patient died on Dec. 20, 1955. The autopsy failed to add any significant new renal findings.

CASE 26 (Table 5).—A 6-year-old boy was stung by a bee in May, 1952, and one week later developed generalized edema. He had not been seriously ill previously and had never had recognized renal symptomatology. There was a rather impressive family history of allergy, and it was noted that a paternal aunt had had several severe "reactions" (generalized edema, unconsciousness) to bee stings.

The boy was admitted to a hospital, where the diagnosis of nephrosis was confirmed and treatment was instituted. Although the degree of edema varied with "spontaneous" diuresis and with therapy (intravenous albumin, cortisone), albuminuria, hypoalbuminemia, hypercholesteremia, and elevation of the ESR were always present during the subsequent 15 months and frequent readmissions to the hospital were necessary. His blood pressure was occasionally elevated, but the average readings obtained were within the normal limits of variation.

He was admitted to the University of Minnesota Hospitals in August, 1953. The physical examination revealed marked generalized edema, pallor, hypertension (B. P. 155/120 mm. Hg), and left pleural effusion.

The laboratory findings included 4+ albumin and and 1+ casts in a routine urinalysis, BUN was 14 mg. %; serum albumin, 0.5 gm. %; serum cholesterol, 678 mg. %, and ESR, 112 mm. in an hour. An Addis count of a 12-hour urine specimen revealed 3.4 gm. of protein, 15,000,000 RBC, and 1,000,000 WBC. The phenolsulfonphthalein (PSP) excretion was 32% in two hours. A urea clearance test was 12.6 cc. per minute, or 23% of the expected normal value for a child of this surface area.

He was treated with mechlorethamine, and a marked diuresis occurred, but there was little change in the laboratory signs of the disease.

Four additional hospital admissions were necessary during the next two years. Transient improvement occurred after repeated courses of mechlorethamine, infection with malaria, and prolonged courses of cortisone and corticotropin. "Spontaneous" diuresis followed intercurrent infections of measles and mumps.

He was admitted for the sixth time in December, 1955, at the age of 10 years, and three one-half years after onset of the nephrotic syndrome. Moderate edema and hypertension were the only significant physical abnormalities. Urinalyses revealed 2+ albuminuria; the serum albumin was 0.9 gm. %; the serum cholesterol, 817 mg. %; the ESR, 61 mm. in an hour, and the BUN, 24 mg. %. An Addis count of a 12-hour urine specimen contained 9,000,000 RBC, 5,000,000 WBC, and 2.0 gm. of protein. His renal function as measured by the clearances of inulin and *p*-aminohippurate (PAH) was approximately 70% of normal.

A renal biopsy specimen was obtained, and microscopic sections of this tissue revealed moderately severe hyalinization and fibrosis of the majority of the glomeruli. In an occasional glomerulus, segmental capillary occlusion by fibri-

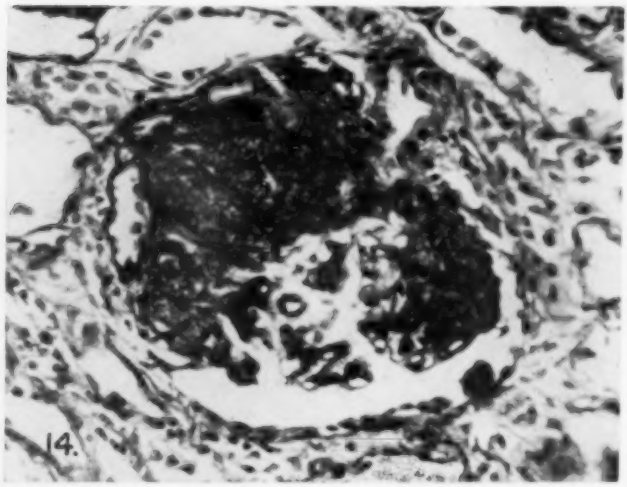


Fig. 14.—Masses of fibrinoid material in a glomerulus from a child with bee-sting nephrosis (Case 26, Table 5). Periodic acid-Schiff stain; × 400.

noid material was a striking feature of this biopsy specimen. An occasional epithelial crescent, minimal tubular atrophy, and interstitial round-cell infiltration were also noted (Fig. 14).

He was treated with cortisone for 14 days and lost 12 lb. of edema fluid. A rise in the serum albumin to 1.9 gm. %, a decline in serum cholesterol to 400 mg. %, a decrease in albuminuria to 1+, and return of the ESR to a near-normal value (28 mm. in an hour) accompanied this diuresis. He was discharged with instructions to take cortisone on three days of each week at home.

He was followed in the outpatient department until March, 1957, while receiving steroid therapy. Although the laboratory evidence of nephrosis persisted at every visit, he remained relatively edema-free. His hypertension was controlled to some extent by antihypertensive drugs. The renal disease progressed to a fatal termination with uremia in April, 1957.

CASE 17 (Table 5).—In 1951 a 5-year-old boy became ill with fever and a sore throat. Periorbital edema followed by generalized edema and ascites developed during the acute illness. A diagnosis of nephrotic syndrome was made, and therapy was instituted, with minimal improvement. Intermittent severe edema and constant proteinuria recurred over the subsequent three years.

He was admitted to the University Hospitals in 1954 with an exacerbation of severe edema. The physical examination was otherwise negative. Laboratory studies revealed 2+ albuminuria, erythrocyte sedimentation rate of 105 mm. in an hour, serum albumin of 0.3 gm. %, serum globulin of 3.3 gm. %, and serum cholesterol of 498 mg. %. The blood urea nitrogen was 10 mg. %. Renal clearance of inulin was 156 cc. per minute per 1.73 square meters of surface area.

Treatment with corticotropin was followed by a loss of 17 lb. of body weight and return of all laboratory findings to normal in the subsequent two months.

The patient was treated with cortisone on three days of each week during the next two years. He remained entirely well.

Repeat studies in 1956, including repeated Addis counts of 12-hour urine specimens, were normal. A renal biopsy specimen obtained at this time revealed a questionable increase in cellularity but was otherwise normal (Fig. 15a).

The hormone therapy was discontinued in September, 1956. Edema, proteinuria, hypercholesteremia, and hypoproteinemia recurred in January, 1957. A second kidney biopsy specimen was obtained at this time, which showed no significant new morphologic features when compared with the biopsy specimen obtained in September, 1956 (Fig. 15b).

The patient was retreated with adrenal hormones and again has been "well" for a period of one year.

Comment

Clinical data on 31 cases of the nephrotic syndrome in childhood have been presented. Cases are included which may be classified clinically as (1) "pure" nephrosis, (2) mixed nephrosis-nephritis, (3) the nephrotic syndrome in chronic glomerulonephritis, (4) nephrosis following a bee sting, (5) familial nephrosis, and (6) the nephrotic syndrome in infancy. The renal pathology of the nephrotic syndrome has been studied by kidney biopsy in each of the cases and in each of the clinical cate-

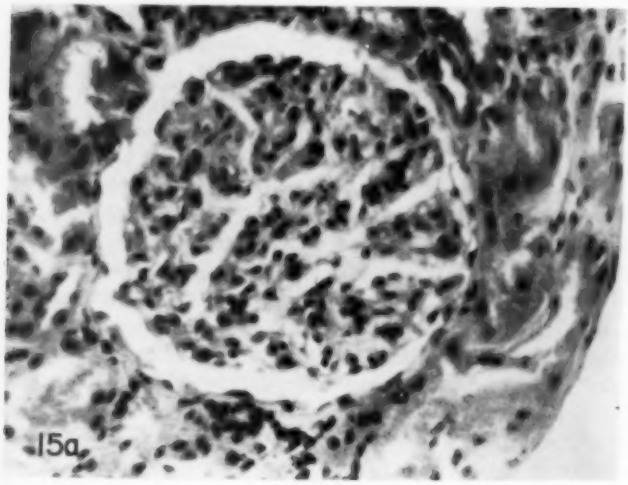


Fig. 15a.—Minimal hypercellularity in a glomerulus from a child whose nephrosis was in clinical remission (Case 17, Table 5). The majority of glomeruli seen were entirely normal. Hematoxylin and eosin stain; ×400.

gories above. A small series of cases in which clinical and laboratory evidence of recovery from the nephrotic syndrome has been obtained has also been studied by renal biopsy and will be discussed below.

Microscopic study of the renal biopsy specimens from most of the children with "pure" nephrosis revealed no significant abnormalities of the kidney. Light microscopic examination of the renal glomerulus, with use of azocarmine and periodic acid (Schiff) stains, failed to reveal significant changes in the capillary basement membranes, or any other glomerular pathology. Occasionally the proximal tubular cells were noted to contain fatty droplets, and frequently protein casts were noted in the lumen of the tubules. These changes are considered to be secondary to increased glomerular filtration of lipid and protein substances.[24]

A smaller number of the cases of "pure" nephrosis were shown by kidney biopsy to have proliferative glomerulonephritis. The earliest evidence of proliferation of the endothelial cells of the glomerular capillaries

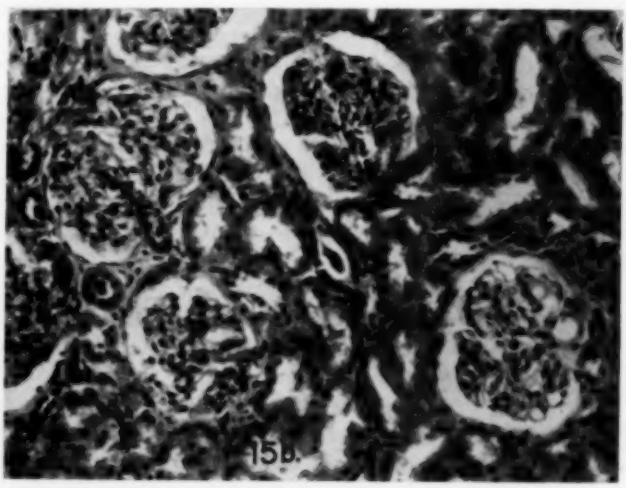


Fig. 15b.—Glomeruli seen in a kidney biopsy specimen obtained five months later, when a severe clinical nephrotic syndrome was present. Hematoxylin and eosin stain; ×110.

in the cases of "pure" nephrosis was associated with pyknosis of the nuclei of the endothelial cells. The glomeruli were often somewhat enlarged, and an occasional segmental area of glomerular capillary hyalinization and fibrosis was noted. In a few of the cases the degree of endothelial proliferation was severe, resulting in relative glomerular ischemia, similar to the morphologic changes in acute glomerulonephritis.

We have thus far had the opportunity to study the serial pathologic changes by renal biopsy in four cases of "pure" nephrosis. In Case 1, Table 5, which has been considered clinically to be "pure" nephrosis, throughout the course of the disease, three kidney biopsy specimens were obtained. The first biopsy specimen was obtained at the peak of clinical expression of the disease and revealed the pathologic changes of minimal proliferative nephritis. The second biopsy specimen was obtained after a dramatic clinical and laboratory remission of the disease had occurred, but no significant changes in the morphology of the renal lesion were apparent. The third biopsy specimen was obtained eight months after the first, at a time when resistance to therapeutic efforts was evident, even though none of the clinical or laboratory criteria for the diagnosis of "nephritis" were present. A striking increase in the degree and type of pathologic glomerular alteration was noted on microscopic study of this specimen. Segmental glomerular fibrosis, epithelial-cell crescent formation, fibrinoid occlusion of the glomerular capillaries, moderate interstitial round-cell infiltration, and tubular atrophy were observed. Three additional patients have shown similar progression of the renal lesion.

The progression of the pathologic changes in this case from minimal proliferative glomerulonephritis to early chronic glomerulonephritis occurred over an interval of eight months. We interpret these findings as evidence supporting the concept suggested by physiologic [41] and clinical data [37] that nephrosis is a single type of disease in which the signs of nephritis, hypertension, and renal insufficiency may appear.

Further support for this concept was obtained by study of cases of "mixed" nephrosis-nephritis and the nephrotic syndrome in chronic glomerulonephritis. All of these patients, except one (Case 22, Table 5), are children who earlier had "pure" nephrosis but in whom hypertension, hematuria, or some degree of renal insufficiency had developed by the time of the renal biopsy. The microscopic pathologic findings revealed by kidney biopsy in these cases were characterized by glomerular fibrosis and hyalinization, epithelial crescents, capillary fibrinoid thrombi, interstitial cellular infiltration, and tubular atrophy. The pathologic diagnosis was compatible with either subacute or chronic glomerulonephritis.

The cases in which the pathologic changes of glomerular fibrosis and capillary obstruction were prominent were those in which nephrosis had been active for relatively long intervals. The correlation between the duration of the disease and the severity of the pathologic alteration is not absolute, however, since in two instances (Cases 13 and 15, Table 5) "pure" nephrosis was present for long intervals and yet minimal morphologic changes were observed in the renal biopsy specimen. In another case (Case 22, Table 5) severe chronic glomerular changes were present in a child with nephrosis of very short duration.

It seems likely that the degree and type of renal pathology in nephrosis in childhood, as revealed by the light microscope, is related to both the duration and the severity of the disease process in a given child. It should be emphasized that we believe that the pathologic terms subacute and chronic glomerulonephritis are descriptive of a recognized pattern of morphologic alteration of the kidney and that no clinical or etiologic significance should

be implied by the use of these terms in the description of the renal lesions of nephrosis.

The two cases of nephrosis which are described as resulting from bee stings are clinically indistinguishable from other cases of the nephrotic syndrome of similar duration. The pathologic renal lesions in these cases, while not distinctly different from the lesion of the nephrotic syndrome in chronic glomerulonephritis, are associated with a striking degree of fibrinoid thrombotic capillary occlusion. The significance of this possible difference in the appearance of the renal lesion in "bee sting" nephrosis and in idiopathic nephrosis is not known.

Familial nephrosis as we have observed it[48] cannot be distinguished from the nephrotic syndrome as it occurs sporadically. Among four children in a single family whom we have studied and for whom we can postulate a single etiologic and pathogenic mechanism, we have found the entire clinical and pathologic spectrum observed in sporadic nephrosis. The clinical manifestations in these children included transient "pure" nephrosis, persistent "pure" nephrosis, mixed nephrosis-nephritis, and chronic glomerulonephritis. The pathological spectrum, as revealed by light microscopy, included normal kidneys in two children, proliferative nephritis in one, and chronic glomerulonephritis in the other. In these children the severity of the pathologic changes appeared to be related to the duration of the disease process. The data available from our study of familial nephrosis would, thus, seem to support the concept that nephrosis is a single type of nephron disease.

Although evidence is as yet insufficient to establish the linear relationship between duration of nephrosis and the extent of the renal pathologic changes, the data from the present series seem to justify a preliminary expression of this concept. It would seem that this concept might be useful in determining the prognosis in this disease in childhood.

1. If the nephrotic syndrome has been active for a long interval (two years or more), it is likely that severe pathologic renal changes have occurred. (This premise is supported with a few exceptions by the renal biopsy data obtained in the present study.)

2. Clinical and laboratory evidence of "recovery" from nephrosis has occurred in this series in only those children who were shown on biopsy to have minimal renal changes. The term "recovery" must be used with uncertainty, however, since sufficient time has not yet elapsed to be certain of recovery. For example, four children have recently developed the clinical signs of a relapse of the disease after a remission of one to two years.

3. Clinical "recovery" may occur in patients who have the pathologic renal lesion designated proliferative nephritis, but clinical recovery has not been observed once the fibrotic changes, termed chronic glomerulonephritis, have become evident.

Glomerular Changes Observed with the Electron Microscope in Children with Diffuse Renal Vascular Disease

The delineation of the fine structure of the normal renal glomerulus in a variety of mammals and man[52-54] and the availability of renal biopsy tissue has made it possible to investigate the ultramicroscopic pathology of renal diseases. A detailed report on the glomerular changes seen in nephrosis, glomerulonephritis, and disseminated lupus erythematosus is available elsewhere.[55,56] A brief description of the structure of the normal glomerulus and of the glomerular changes seen in diffuse renal vascular diseases is included in this report in order to correlate the electron microscopic observations with clinical findings and observations based on light microscopy.

The Normal Renal Glomerulus.—Although controversy exists regarding details of fine glomerular structure, it is generally agreed that the glomerular capillary has three distinct components—the endothelium,

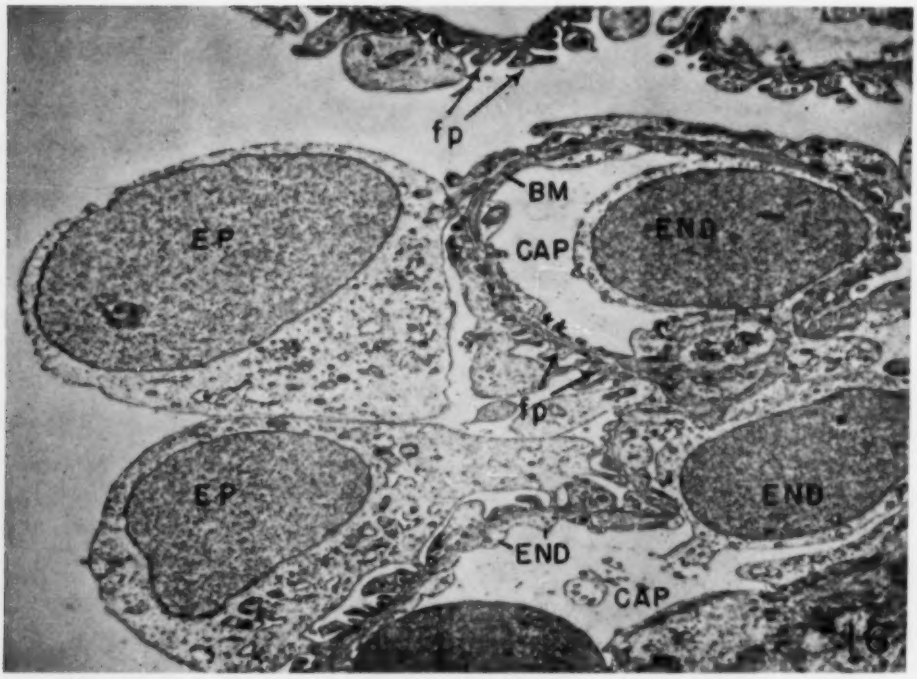


Fig. 16.—Normal glomerular capillary organization. Two epithelial cells occupy the left half of the field. The primary processes of the epithelial cells and the insertion of the secondary "foot processes" upon the basement membrane are shown. Note the increased density of the foot processes adjacent to the basement membrane. An endothelial cell fills most of the lumen of the capillary to the right. The thin attenuated cytoplasm of the endothelial cell lines the inside of the capillary, and characteristic interruptions are visible (arrows). The central dense zone and the lighter peripheral zones of the basement membrane can be seen clearly in several areas; × 7000. Abbreviations for figures are as follows: *END*, endothelium; *BM*, basement membrane; *EP*, epithelial cell; *RBC*, red blood cell; *CAP*, capillary; *fp*, foot process; *vac*, vacuole; *fib*, fibrinoid.

the basement membrane, and the epithelium (Fig. 16).

The endothelial cells lie adjacent to the lumen of the capillary. They are more numerous than epithelial cells, and their nuclei are somewhat smaller and denser than those of the latter. The cytoplasm of the endothelial cell becomes attenuated away from the cell body, forming a thin layer which covers the inner wall of the basement membrane. This thin layer of endothelial cytoplasm appears to contain numerous very small interruptions which are thought by a number of investigators to represent endothelial "pores."

The basement membrane proper, or "lamina densa" of Hall,[57] is a relatively homogeneous layer, approximately 0.15μ to 0.20μ in total thickness, varying somewhat with age and species. It is relatively dense centrally but is separated from the endothelium on the inner side and from the epithelium on the outer side by thin, less dense zones thought to represent either areas of cement substance[58] or integral parts of the basement membrane.[59]

The epithelial cells are the outermost component of the glomerular capillary wall and have a very complex structure. The cytoplasm of each epithelial cell branches into a number of primary processes which in turn form numerous secondary "foot processes" which insert upon the outer aspect of the basement membrane proper.

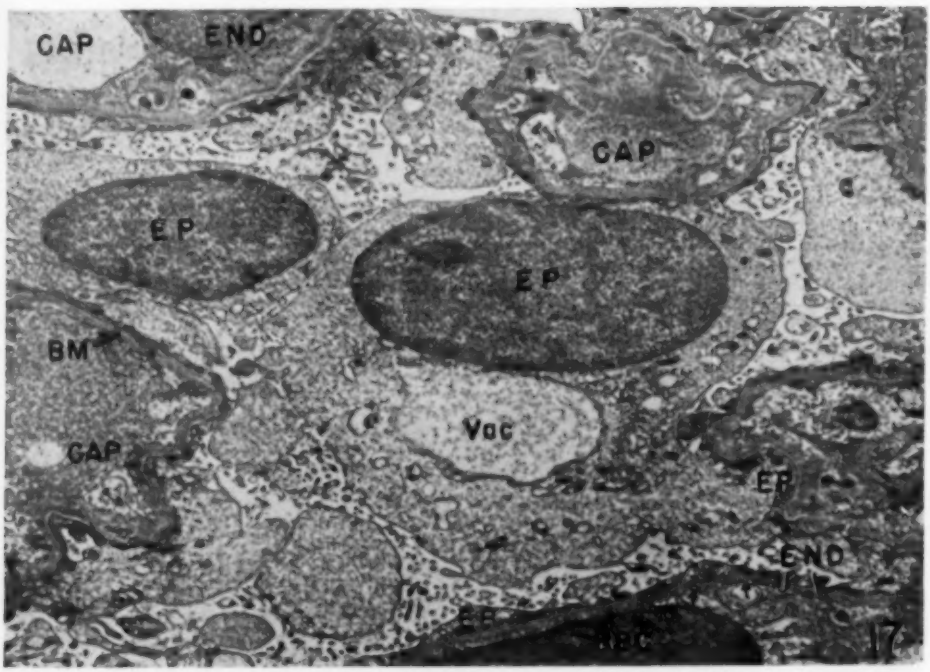


Fig. 17.—Nephrotic syndrome (Case 11, Table 5). The epithelial cells which send processes to several adjacent capillary loops are located centrally. Note that foot processes are absent and that the peripheral cytoplasm of the epithelial cells extends along the capillary basement membrane as an uninterrupted layer. Precipitated serum protein obscures the thin endothelial cytoplasm in many areas, but, where visible (arrows), the endothelium is normal. The basement membrane is essentially normal; × 7000. Abbreviations are the same as in Figure 16.

A clear space separates the adjacent foot processes at the point of their contact with the basement membrane. The terminal area of each foot process, where it contacts the basement membrane, is distinctly denser than the remainder of the epithelial cytoplasm.

Electron Microscope Observations in the Nephrotic Syndrome.—Renal tissues from 27 of the children listed in Table 5 were studied by electron microscopy. A striking abnormality of the epithelial cell was seen in every case of nephrosis examined to date. The abnormality consisted of loss of the foot processes, resulting in smudging of epithelial cytoplasm along the basement membrane. Only infrequent interruptions were visible between the masses of foot-process material (Fig. 17). The degree of foot-process "smearing" varied from patient to patient and from one glomerulus to another from the same patient. Occasionally some variation was noted among the capillary loops in a given glomerulus. The abnormality was severer in those patients who showed clinical "pure" nephrosis and in whom light microscopy revealed normal glomeruli. In addition, increased numbers of cytoplasmic vacuoles were frequently observed in the epithelial cells from patients who had the nephrotic syndrome. Endothelial vacuoles were also often noted along with a swelling and ballooning of endothelial cytoplasm.

Additional abnormalities were regularly observed in the glomeruli from patients who were classified clinically as having "mixed" nephrosis-nephritis and in whom the light microscopic diagnosis of subacute or chronic glomerulonephritis was suggested. These biopsy specimens showed endothelial-cell proliferation and abnormali-

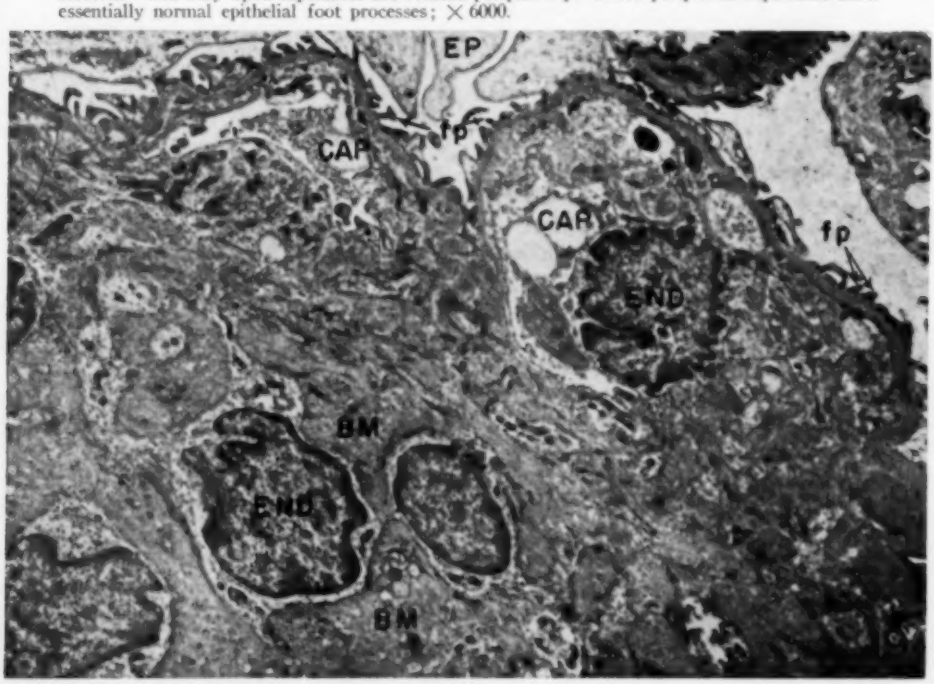
Fig. 18.—Acute glomerulonephritis (Case 2, Table 4). The dominant morphologic features illustrated are proliferation and swelling of the endothelial cells, which has resulted in obliteration of many of the capillary lumina. The cytoplasm of the epithelial cells is also swollen, though to a less extent. The epithelial-cell foot processes are relatively intact. The basement membranes are moderately thickened, and an accumulation of basement-membrane-like material is seen intermingled with endothelial cytoplasm; reduced about 3% from mag. × 8100. Abbreviations are the same as in Figure 16.

ties of the basement membrane. Changes in the basement membrane included both uniform and nodular thickening and occasional areas of inhomogeneity. A striking feature seen in the severer cases was an accumulation of material which resembled basement membrane. This material was intimately related to the cytoplasm of endothelial cells, extending in broad sheets and bands which often encroached considerably on the luminal area of the capillary loop. Electron microscopy of renal biopsy specimens from three children with nephrosis in complete clinical remission showed them to be normal. This observation indicates that the epithelial-cell foot-process abnormality described above is reversible.

Electron Microscopic Observations in Glomerulonephritis.—Renal biopsy specimens from 11 of the cases of glomerulonephritis listed in Table 4 have been studied by electron microscopy. The prominent abnormalities observed were proliferation of endothelial and epithelial cells, broadening of peripheral endothelial cytoplasm, and accumulation of basement-membrane-like material between the endothelial cells. Proliferation of the endothelium was particularly striking in the cases of acute glomerulonephritis (Fig. 18). The increased numbers of endothelial cells and of trapped cells apparently derived from the blood, together with the swelling of the endothelial cytoplasm, resulted in nearly complete occlusion of the lumina of many glomerular capillaries.

In addition to proliferative changes, the glomeruli from cases of subacute and chronic glomerulonephritis (Fig. 19) showed varying degrees of basement membrane thickening and accumulations of masses of basement-membrane-like material which encroached on the capillary lumina.

Fig. 19.—Chronic glomerulonephritis (Case 11, Table 4). In this severely damaged glomerulus, the more central capillaries are occluded by accumulations of basement-membrane-like material. The only open capillaries are located peripherally. These peripheral capillaries show essentially normal epithelial foot processes; × 6000.



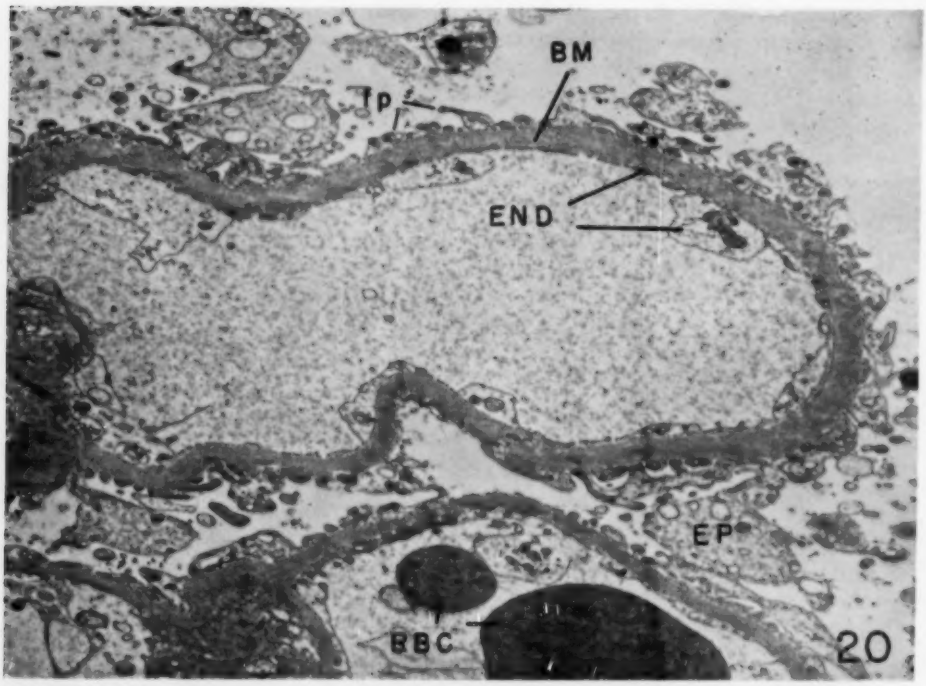


Fig. 20.—Portions of two capillary loops from the kidney of a child with disseminated lupus erythematosus (Case 2, Table 3). The basement membranes are thickened to approximately 4350 A. in total thickness, in contrast to the normal basement membrane (Fig. 16), which is 1450 A. in total thickness. The endothelium and epithelium are essentially normal; × 6500.

The form of this material varied from bands of apparently newly formed basement membrane interlaced with endothelial cytoplasm to masses which completely obliterated some capillary loops. These severely involved glomeruli undoubtedly correspond to hyalinized or partially hyalinized glomeruli recognized by light microscopy.

The epithelial-cell foot processes were generally normal in all phases of the disease process except in those areas of severe damage where it was often impossible to distinguish clearly between the three components of the capillary wall.

Electron Microscopic Observations in Disseminated Lupus Erythematosus.—Our observations on the ultramicroscopic glomerular pathology in disseminated lupus erythematosus are derived from the study of renal biopsy specimens from four of the five children listed in Table 30. The principal abnormalities noted were a thickening of the basement membrane and a proliferation of endothelial cells (Fig. 20). Some glomeruli showed only a minimal basement membrane thickening apparent in the more peripheral capillary loops. In other, more severely damaged, glomeruli, the basement membrane was six to eight times the normal width. Glomeruli from those cases of short duration, in which minimal changes were noted by light microscopy, characteristically showed only basement membrane thickening and endothelial proliferation, while the more severely involved glomeruli from the most advanced cases revealed accumulations of basement membrane material as well as basement membrane thickening.

The epithelium did not appear to be significantly altered in the renal biopsy speci-

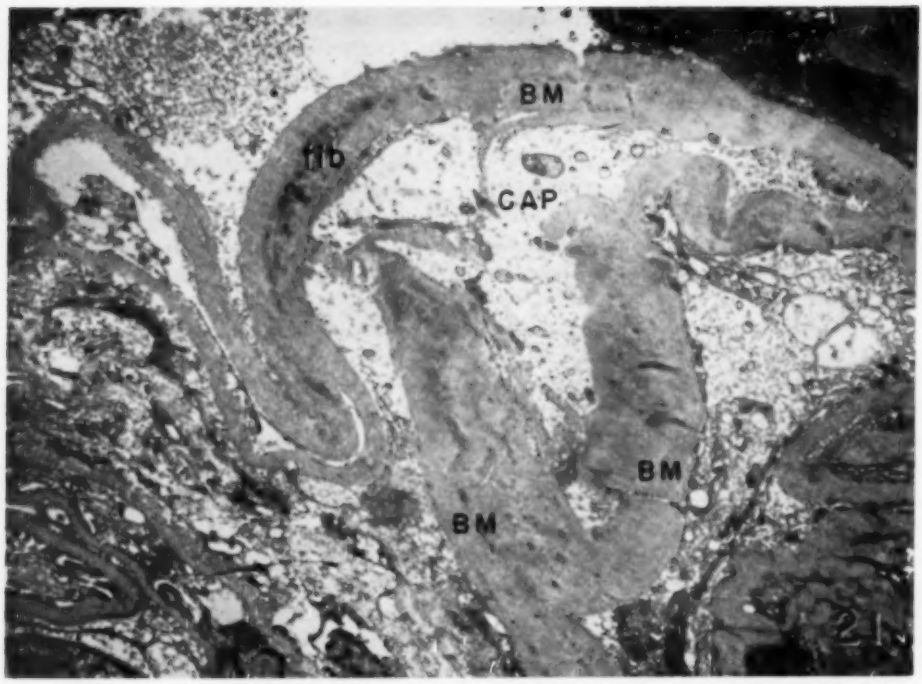


Fig. 21.—Severely damaged capillary loops from the kidney of a child with disseminated lupus erythematosus (Case 4, Table 3). The extreme thickening of the basement membranes shown here probably represents the wire-loop lesion. The dense granular material which contributes to the thickening of the basement membrane at the top of the Figure is believed to be fibrinoid; × 6000. Abbreviations are the same as in Figure 16.

mens obtained early in the course of the disease process. Distortion of the epithelial foot processes became evident only when the basement membrane was greatly thickened.

A dense homogeneous material, which differed morphologically from basement membrane, was noted in two cases of disseminated lupus erythematosus. This dense material is believed to correspond to "fibrinoid" and was located between the basement membrane and the endothelium (i. e., was subendothelial).

In one of the patients with disseminated lupus erythematosus, typical wire-loop lesions were seen by light microscopy. By electron microscopy, the glomeruli from this patient showed greatly thickened basement membranes associated with a subendothelial layer of fibrinoid and/or basement-membrane-like material (Fig. 21). These changes produced a dense, thickened capillary wall which probably corresponds to the wire-loop lesion seen by light microscopy.

Electron Microscopic Observations in Anaphylactoid Purpura.—Renal biopsy specimens from four patients who clinically had anaphylactoid purpura with a form of glomerulonephritis have been studied by electron microscopy. The lack of uniformity of the abnormalities noted in the few specimens studied to date does not permit generalizations as to the significance of the changes observed. Further study of this form of renal disease is in progress.

Comment.—A description of the glomerular changes revealed by electron microscopy of 42 renal biopsy specimens from children with glomerulonephritis, the nephrotic syndrome, and disseminated lupus erythematosus has been presented. The

three distinct components of the glomerular capillary wall were found to be differentially involved in the three disease processes. The principal glomerular abnormality observed in the nephrotic syndrome and the only abnormality seen in early or "pure" nephrosis is a marked loss or smudging of epithelial-cell foot processes. These changes were present in every case of the nephrotic syndrome studied, regardless of the duration or the clinical severity of the disease process and regardless of the light microscopic pathology. Abnormalities of the foot processes have not been seen as an early manifestation in cases of anaphylactoid purpura, glomerulonephritis, or disseminated lupus erythematosus.

These observations suggest that the foot-process abnormality is either the cause or the result of the severe proteinuria and the associated chemical and laboratory abnormalities of the nephrotic syndrome.

Our findings also suggest that the epithelial cell may be the site of early injury to the glomerulus in nephrosis. However, an alternative, equally attractive hypothesis is that the nephrotic syndrome develops as a result of some basement membrane abnormality which has not yet been defined. The foot-process lesion could then be a secondary response to a basement membrane injury.

It should be recalled that many of the kidney biopsy specimens studied in this investigation appeared "normal" when evaluated by light microscopy; yet these same biopsy specimens invariably revealed severe epithelial foot-process abnormalities when studied by electron microscopy. This is understandable, since the epithelial-cell foot processes are not visible by light microscopy. The thickened "basement membrane" which has been described [24] as the characteristic glomerular abnormality observed by light microscopy in the nephrotic syndrome probably represents a capillary wall in which there have been varying degrees of foot-process flattening, basement membrane thickening, and broadening of the peripheral endothelial cytoplasm.

The endothelial proliferation, changes in the basement membrane, and accumulation of masses of basement-membrane-like material, noted frequently in more severely diseased glomeruli from cases of "mixed" nephrosis-nephritis and cases of the nephrotic syndrome in chronic glomerulonephritis, may be thought to represent complications of nephrosis which are related to the duration and severity of the disease process. These advanced changes correspond to the endothelial proliferation and hyalinization which can be seen and evaluated by light microscopy.

Electron microscopy of glomeruli from patients with glomerulonephritis revealed the principal abnormalities to be a pronounced proliferation of endothelial cells, some proliferation of epithelial cells, and an accumulation of basement-membrane-like material. Early in the course of glomerulonephritis, the epithelial-cell foot processes appeared normal.

In the subacute and chronic forms of glomerulonephritis, severer degrees of basement membrane proliferation were observed. The most severely damaged glomeruli were composed of endothelial nuclei enmeshed within masses of abnormal basement-membrane-like material. Such glomeruli correspond to the hyalinized or partially hyalinized glomeruli seen by light microscopy.

Electron microscopy of kidney biopsy specimens obtained early in the clinical course of acute disseminated lupus erythematosus revealed basement membrane thickening and variable degrees of endothelial proliferation. The basement membranes of glomeruli from two patients with advanced renal disease were thickened to at least six to eight times the normal width. Our observations suggest that the severity of the basement membrane involvement in disseminated lupus erythematosus is related to the duration of the disease process. Abnormal-

ities of the epithelial cells were encountered only late in the course of the disease.

Severe basement membrane thickening and splitting, together with an accumulation of a subendothelial layer of dense "fibrinoid" material, would seem to represent the wire-loop lesions described by light microscopy.

Summary

An application of renal biopsy to the study of diffuse renal vascular disease in 58 children is presented. Needle biopsy of the kidney was found to be a safe, relatively atraumatic procedure in children, worthy of extensive use as an investigative technique.

Light microscopy revealed the renal lesion of anaphylactoid purpura to be segmental glomerulitis characterized by occlusion of lobules of the glomeruli by fibrinoid material. The glomerular lesion observed in anaphylactoid purpura is similar to an abnormality often seen in disseminated lupus erythematosus, and it is suggested that anaphylactoid purpura probably should be classified as a systemic fibrinoid vascular disease.

The characteristic pathologic abnormalities observed in kidney biopsy specimens from children with disseminated lupus erythematosus varied from segmental vascular fibrinoid lesions to severe glomerulonephritis. Serial biopsies in three children treated with intensive prolonged corticosteroid therapy confirmed the clinical and laboratory evidence of improvement in renal disease during the interval of treatment. Renal biopsy may occasionally aid in the confirmation of the diagnosis of disseminated lupus erythematosus when other evidence is inconclusive.

The clinical and pathologic features of acute, subacute, and chronic glomerulonephritis are reviewed. Evidence supporting the concept that acute streptococcal nephritis is an entity separate from subacute or chronic glomerulonephritis is presented.

The pathologic findings obtained by kidney biopsies in patients with the nephrotic syndrome are correlated with the clinical and laboratory features of the disease. We conclude that the pathology of nephrosis is related to the duration and the severity of the disease.

The ultramicroscopic morphology of the normal kidney and the glomerular pathology of nephrosis, glomerulonephritis, and disseminated lupus erythematosus are briefly reviewed. The three layers of the glomerular capillary wall, the endothelium, lamina densa, and epithelium appear to be differently involved early in the course of each of these diseases. The smudging of the epithelial-cell foot processes observed in patients with nephrosis is reversible, and the glomerulus is normal by electron microscopy during complete clinical remission. The possible etiologic and physiologic significance of the submicroscopic pathology revealed by the electron microscope is discussed.

Dr. Julian Ansell, Department of Urology, University of Minnesota, performed some of the early kidney biopsies. Miss Donna Jensen, Mrs. Marilyn Wolcott (light microscopy), Mrs. Karen Taylor, Mr. Richard Condie, and Mr. Robert Brooks (electron microscopy) gave technical assistance.

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REFERENCES

1. Palade, G. E.: A Study of Fixation for Electron Microscopy, J. Exper. Med. 95:285, 1952.

2. Newman, S. B.; Borysko, E., and Swerdlow, M.: Ultra-Microtomy by a New Method, J. Res. Nat. Bureau of Standards 43:183, 1949.

3. Porter, K. R., and Blum, J.: A Study in Microtomy for Electron Microscopy, Anat. Rec. 117:685, 1953.

4. Latta, H., and Hartman, J. F.: Use of Glass Edge in Thin Sectioning for Electron Microscopy, Proc. Soc. Exper. Biol. & Med. 74:436, 1950.

5. Runge, W.; Vernier, R. L., and Hartmann, J. F.: A Staining Method for Sections of Osmium-Fixed, Methacrylate-Embedded Tissues, J. Biochem. & Biophys. Cytol. 4:327, 1958.

6. Farquhar, M. G.: Preparation of Ultrathin Tissue Sections for Electron Microscopy, Lab. Invest. 5:317, 1956.

7. Muehrcke, R. C.; Kark, R. M., and Pirani, C. L.: Technique of Percutaneous Renal Biopsy in Prone Position, J. Urol. 74:267, 1955.

8. Muehrcke, R. C.; Kark, R. M., and Pirani, C. L.: Biopsy of the Kidney in the Diagnosis and Management of Renal Disease, New England J. Med. 253:537, 1955.

9. Osler, W.: The Visceral Lesions of Purpura and Allied Conditions, Brit. M. J. 1:517, 1941.

10. Oliver, T. K., Jr., and Barnett, H.: The Incidence and Prognosis of Nephritis with Anaphylactoid (Schönlein-Henoch) Purpura in Children, A. M. A. Am. J. Dis. Child. 90: 544, 1955.

11. Philpott, M. G.: Anaphylactoid Purpura in Children with Particular Reference to the Occurrence of Nephritis, Arch. Dis. Childhood 27:480, 1952.

12. Wedgewood, R., and Klaus, M.: Anaphylactoid Purpura (Schoenlein-Henoch Syndrome), Pediatrics 16:196, 1955.

13. Panos, T.: Mesenchymal Diseases of Childhood: Report of the 22d Ross Pediatric Research Conference, Columbus, Ohio, Ross Laboratories, 1957, p. 88.

14. Colle, E. C.; Vernier, R. L., and Good, R. A.: A Study of the Etiology and Pathogenesis of Anaphylactoid Purpura, to be published.

15. Simpkiss, M. J.: Henoch-Schönlein Syndrome, Great Ormond St. J., pp. 7-12, June, 1953.

16. Derham, R. J., and Rogerson, M. M.: The Schoenlein-Henoch Syndrome with Particular Reference to Renal Sequela, Arch. Dis. Childhood 31:364, 1956.

17. Clark, R., and Jacobs, I.: Experimental Non-Thrombopenic Vascular Purpura: A Review of the Japanese Literature with Preliminary Confirmatory Report, Blood 5:320, 1950.

18. Lewis, I. C.: The Schoenlein-Henoch Syndrome Compared with Certain Features of Nephritis and Rheumatism, Arch. Dis. Childhood 30:222, 1955.

19. Levitt, J. M., and Burbank, B.: Glomerulonephritis as a Complication of Henoch-Schoenlein's Syndrome, New England J. Med. 248:530, 1953.

20. Medal, L. S., and Reynoso, E.: Anaphylactoid Purpura (Henoch-Schoenlein's Disease): Clinical Study of 45 Cases, Rev. invest. clin. 7:293, 1955.

21. Andrews, V. M.: Antistreptolysin-O Titers in Allergic Purpura and Related Diseases, Am. J. M. Technol. 20:97, 1954.

22. Jacobson, W. E.: The Effect of A. C. T. H. on the Nephropathy of Disseminated Lupus Erythematosus, Minn. Med. 35:541, 1951.

23. Dubois, E. L.; Commons, R. R.; Starr, P.; Stein, C. S., Jr., and Morrison, R.: Corticotropin and Cortisone Treatment for Systemic Lupus Erythematosus, J. A. M. A. 149:995, 1952.

24. Bell, E. T.: Renal Disease, Philadelphia, Lea & Febiger, 1956.

25. Muehrcke, R. C.; Kark, R. M.; Pirani, C. L., and Pollak, V. E.: Lupus Nephritis: Clinical and Pathologic Study on Renal Biopsies, Medicine 36:1-145, 1957.

26. Addis, T.: Glomerulonephritis: Diagnosis and Treatment, New York, The Macmillan Company, 1948.

27. Stetson, C. A.; Rammelkamp, C. H., Jr.; Krause, R. M.; Kohen, R. J., and Perry, W. D.: Epidemic Acute Nephritis: Studies on Etiology, Natural History and Prevention, Medicine 34:431, 1955.

28. Rytand, D. A., and Randull, E.: Titers of Heterophila Antibodies and Anti-Streptolysin "O" in Acute Glomerular Nephritis and in the Nephrotic Syndrome, Am. J. Med. 8:524, 1950.

29. Rammelkamp, C. H., Jr.: Glomerulonephritis, Proc. Inst. Med., Chicago 19:371, 1953.

30. Denny, F. W., Jr.; Perry, W. D.; Wannamaker, L. W., and Rammelkamp, C. H., Jr.: Type Specific Streptococcal Antibodies, J. Lab. & Clin. Med. 44:787, 1954.

31. Earle, D. P., Jr., et al.: The Serum Antistreptolysin Titer in Chronic Glomerulonephritis, J. Clin. Invest. 21:483, 1942.

32. Aldrich, C. A.: Nephritis, in Brenneman's Practice of Pediatrics, Hagerstown, Md., W. F. Prior Company, Inc., 1943.

33. Herbert, H. J.: Acute Glomerulonephritis in Childhood: A Study of the Late Prognosis of 27 Cases, J. Pediat. 40:549, 1952.

34. Seegal, D.; Lyttle, J. D.; Loeb, E. N.; Jost, E. L., and Davis, G.: On the Exacerbation in Chronic Glomerulonephritis, J. Clin. Invest. 19: 569, 1950.

35. Ellis, A.: Natural History of Bright's Disease: Clinical, Histological and Experimental Observations, Lancet 1:34; 72, 1942.

36. Worthen, H., and Vernier, R. L.: Correlation of Renal Biopsies with Renal Function, to be published.

37. Barnett, H. L.; Forman, C. W., and Lauson, H. D.: The Nephrotic Syndrome in Children, in Advances in Pediatrics, Vol. 5, edited by S. Z. Levine, Chicago, The Year Book Publishers, Inc., 1952.

38. Heymann, W.; Gilkey, C., and Lewis, M.: The Prognostic Significance of Globulinuria in the Nephrotic Syndrome, Am. J. Dis. Child. 91:570, 1956.

39. Barness, L. S.; Moll, G. H., and Janeway, C. A.: Nephrotic Syndrome: I. Natural History of the Disease, Pediatrics 5:486, 1950.

40. Mateer, F. M.; Weigand, F. A.; Greenman, L.; Weber, C. J., Jr.; Kunkle, G. A., and Danowski, T. S.: Corticotropin (ACTH) Therapy of Nephrotic Syndrome in Children: I. Clinical Results and Effects of Proteinuria in 106 Instances, A. M. A. J. Dis. Child. 93:591, 1957.

41. Metcoff, J.; Kelsey, W. M., and Janeway, C. A.: The Nephrotic Syndrome in Children:

An Interpretation of Its Clinical, Biochemical and Renal Hemodynamic Features as Variation of a Single Type of Nephron Disease, J. Clin. Invest. 30:471, 1951.

42. Merrill, A. J.; Wilson, J., and Timberlake, L. F.: Continuous Therapy of Nephrotic Syndrome in Children with Corticotropin Gel, A. M. A. Arch. Int. Med. 94:925, 1954.

43. Vernier, R. L.: An Evaluation of Steroid Therapy in 65 Children with Nephrosis, unpublished observations.

44. Volhard, F., and Fahr, T.: Die Brightsche Nierenkrankheit, Berlin, Springer-Verlag, 1914.

45. Ehrich, W. E.; Forman, C. W., and Seifer, J.: Diffuse Glomerular Nephritis and Lipid Nephrosis: Correlation of Clinical, Morphological and Experimental Observations, A. M. A. Arch. Path. 54:463, 1952.

46. Rytand, D. A.: The Nephrotic Syndrome and Chronic Lipoid Nephrosis, unpublished manuscript.

47. McQuarrie, I.: Experiments of Nature, Lawrence, Kan., University of Kansas Press, 1944.

48. Vernier, R. L.; Brunson, J., and Good, R. A.: Studies on Familial Nephrosis: I. Clinical and Pathologic Study of 4 Cases in a Single Family, A. M. A. J. Dis. Child. 93:469, 1957.

49. Farquhar, M. G.; Vernier, R. L., and Good, R. A.: Studies on Familial Nephrosis: II. Glomerular Changes Observed with the Electron Microscope, Am. J. Path. 33:791, 1957.

50. Rytand, D. A.: Onset of the Nephrotic Syndrome During a Reaction to Bee Sting, Stanford M. Bull. 13:224, 1955.

51. Rothenberg, M. B., and Heymann, W.: Incidence of the Nephrotic Syndrome in Children, Pediatrics 19:446, 1957.

52. Rinehart, J. F.: Fine Structure of Renal Glomerulus as Revealed by Electron Microscopy, A. M. A. Arch. Path. 59:439, 1955.

53. Hall, B. V.: Further Studies of Normal Structure of the Renal Glomerulus, in Proceedings of the Sixth Annual Conference on the Nephrotic Syndrome, New York, National Nephrosis Foundation, Inc., 1954, pp. 1-40.

54. Mueller, C. B.; Mason, A. B., and Stout, A. D.: Anatomy of the Glomerulus, Am. J. Med. 18:767, 1955.

55. Farquhar, M. G.; Vernier, R. L., and Good, R. A.: The Application of Electron Microscopy in Pathology: Study of Renal Biopsy Tissues, Schweiz. med. Wchnschr. 87:501, 1957.

56. Farquhar, M. G.; Vernier, R. L., and Good, R. A.: An Electron Microscopic Study of the Glomerulus in Nephrosis, Glomerulonephritis and Lupus Erythematosus, J. Exper. Med. 106:649, 1957.

57. Hall, B. V.: Studies of Normal Glomerular Structure by Electron Microscopy, in Proceedings of the Fifth Annual Conference on the Nephrotic Syndrome, New York, National Nephrosis Foundation, Inc., 1953, p. 1.

58. Pease, D. C.: Electron Microscopy of the Vascular Bed of the Kidney Cortex, Anat. Rec. 121:572, 1955.

59. Yamabe, E.: The Fine Structure of the Renal Glomerulus of the Mouse, J. Biophys. & Biochem. Cytol. 1:551, 1955.

Osteogenesis Imperfecta Associated with Cutaneous Pigmentation and Other Congenital Malformations

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In 1922, Weil [1] referred to the case of a 9-year-old girl whose menarche had commenced at the age of 18 months. The patient had blue sclerae and irregular cutaneous pigmentation and had suffered seven fractures, and, though the article did not reproduce radiological or biopsy reports, it indicated that "the diaphysis is thin, the rest of the bone is not gracile, and it is assumed to be an atypical form of osteopsathyrosis."

These references indicate that this could have been a case of osteogenesis imperfecta with early puberty, cutaneous pigmentation, and blue sclerae, in spite of which it is cited in the important reports by Albright and associates,[2] Robson and Todd,[3] Dockerty and associates,[4] and Stein and associates,[5] among others, as a case of poliostotic fibrous dysplasia.

We have had the opportunity of studying the case of a child whose characteristics bear some resemblance to those of Weil's case.

Report of a Case

A 3-year-old Argentinian girl was referred to us by the orthopedic service, where she was being treated for congenital dislocation of the right hip as a result of which she could not walk without aid. She began to speak at the age of 2, but had difficulty in producing words, hearing being normal. At the age of one year a lumbar scoliosis had been verified.

The gestation period was apparently normal, and there was no consanguinity. Previous family history revealed no other malformation.

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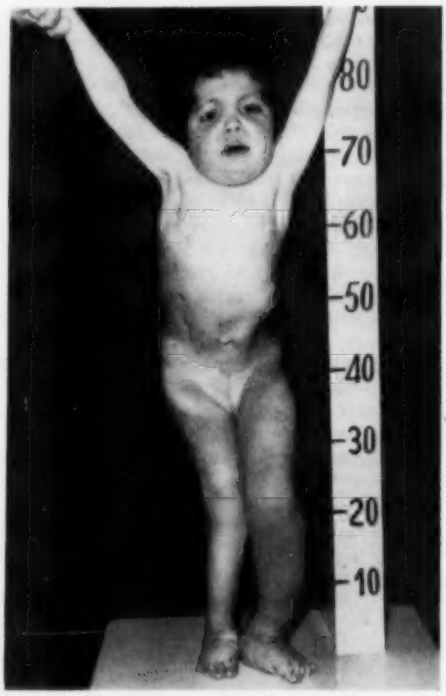

Fig. 1.—The patient, 3 years old.

The patient's gestation was apparently normal. The mother had had a previous premature child (eighth month), who died on the 15th day.

Physical examination showed height to be 81 cm. (Fig. 1). Blue sclerae, mild strabismus, bilateral epicanthic folds, ogival palate, parieto-occipital alopecia, short neck, sternal depression, a globulous abdomen, and lumbar scoliosis were noted.

An extensive area of bilateral café au lait pigmentation was apparent on the skin of abdomen and lower chest, the borders of which were irregular; the upper limit outlined the border of the right 5th rib, descended to the umbilicus, and then coursed up to the angle of the 10th left rib in the axillary line (Fig. 2*A*). The inferior limits extended to approximately 5 cm. over both groins.

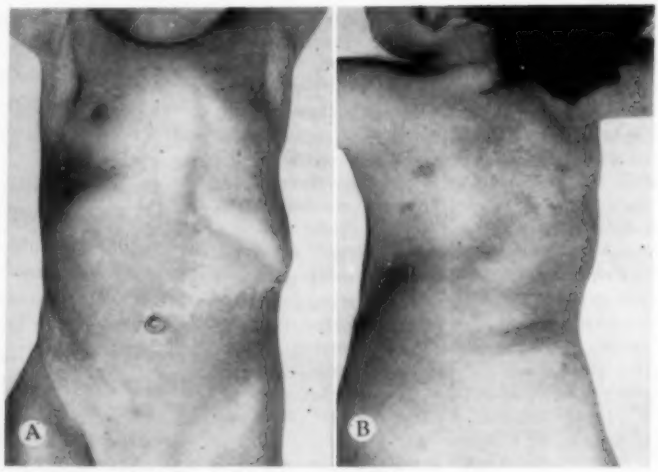

Fig. 2.—Café au lait skin pigmentation of (*A*) abdomen and lower chest and (*B*) the back of the trunk.

The back was covered by an extensive area of pigmentation, the upper limit of which was irregular and extended from the angle of the right axillary line with the fifth rib to the angle of the left axillary line with the eighth rib. There were some isolated areas of pigmentation on both scapulae (Fig. 2*B*). The right thigh was covered with an area of pigmentation which reached the knee, and the left inferior member was completely pigmented.

There was slight hypertrophy of the labia majora and congestion of the vulva.

The lower limbs were asymmetrical and covered with abundant lanugo. There was a reduction in the diameter of the right lower limb, and the left lower limb was hypertrophied. Left tibia vara was present.

Measurements were as follows: span, 87 cm.; top of head to pubis, 50 cm.; pubis to ground, 31 cm.

Fig. 3.—Osteogenesis imperfecta of (*A*) both tibiae and fibulae, with an area of increased density corresponding to the calluses of congenital fractures, and (*B*) bones of the left superior limb.

Fig. 4.—Lumbar scoliosis and congenital dislocation of the right hip.

Figure 3

Figure 4

X-ray of the skeleton showed generalized bone rarefaction with thinning of the diaphyses of the long bones (Fig. 3). A marked curvature of the tibia and fibula was verified in both legs, with an area of increased density in the middle third of the bone, corresponding to the calluses of congenital fractures. Marked lumbar scoliosis and congenital dislocation of the right hip and subdislocation of the left hip were noted. Bilateral coxa valga was present (Fig. 4).

Laboratory Data.—Blood: 4,500,000 red cells; 8200 leukocytes; the differential count showed a high eosinophil count (7.8%). Serum nonprotein nitrogen: 20 mg. per 100 ml. Kahn test, presumptive and standard, was negative. Serum phosphorus: 3.76 mg. per 100 ml. Alkaline serum phosphatase: 3.27 and 3.13 Bodansky units per 100 ml. Serum calcium: 9.4 mg. per 100 ml. Serum potassium: 4.2 mEq. per liter.

Examination of urine revealed a trace of protein and a few red blood cells. The titer of urinary gonadotropins was zero on two determinations. Urinary ketosteroids were 1.9 to 1.15 mg. per 24 hours.

Urinary sediment and vaginal smears indicated development corresponding to age.

Comment

The association of osteogenesis imperfecta with cutaneous pigmentation, slight hypertrophy of the labia majora, blue sclerae, lumbar scoliosis, congenital dislocation of the hip, and parieto-occipital alopecia found in this case, presents, together with the case reported by Weil,[1] a similarity to the syndrome of polyostotic fibrous dysplasia with skin pigmentation and precocious puberty described by Albright and associates.[2]

There is also remarkable similarity to Case 4 in the report by Dockerty and associates,[4] a case of poliostotic fibrous dysplasia, hypertrophy of the right labium majus of the vulva, dorsolumbar scoliosis, and occipital alopecia. Though scoliosis is a frequent complication of osteogenesis imperfecta,[6] it also occurred in the cases of poliostotic fibrous dysplasia described by Robson and Todd,[3] Summerfeldt and Brown,[7] and Stauffer and associates.[8] Similarily, in the case of polyostotic fibrous dysplasia reported by Berardinelli[9] the sclerae were blue, and in Stauffer's case[8] there was deafness, manifestations which are also frequently associated with osteogenesis imperfecta.

The lumbar scoliosis and congenital dislocation of the hip are presumably results of structural deficiencies of mesenchymatous origin.[10]

Though mono- or polyostotic fibrous dysplasia, as well as precocious puberty or skin pigmentation, are more often isolated, it is evident that the association of two or three of these anomalies, to which eventually are added other lesions, is so frequent as to imply a lesion that often affects some distinct segments of the ecto- and mesoderm.[2, 6,9]

Knaggs[11] has considered the factor of heredity in the lesion of the connective tissue cell of the embryo, as well as the incidence of environmental factors. In a review of statistics covering 40 cases, Bickel and associates[12] found that osteogenesis imperfecta was hereditary in 27.5%. Retrospective analysis reveals a 50% incidence of cases apparently hereditary in nature. The hereditary form would appear to be transmitted by a dominant gene, not linked to sex, the abnormality appearing in 50% of the descendants of a couple in which one of the partners is affected.[13] With regard to poliostotic fibrous dysplasia, Albright and Reifenstein[14] showed that it was not hereditary in character, in spite of which Berardinelli[9] refers to cases where heredity played a role. In our patient there was no indication that the disease had been inherited.

It is possible to assume that a genetic or embryological lesion which affects certain segments of the mesoderm and ectoderm could eventually lead to osteogenesis imperfecta or poliostotic fibrous dysplasia, together with other manifestations.

Summary

A girl is described with osteogenesis imperfecta associated with cutaneous pigmentation, slight hypertrophy of the labia majora, blue sclerae, lumbar scoliosis, congenital dislocation of the right hip, and

occipitoparietal alopecia. Comment is made on the similarity of this case to poliostotic fibrous dysplasia associated with malformation, or Albright's syndrome.

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REFERENCES

1. Weil: Pubertas praecox und Knochenbrüchigkeit, Klin. Wchnschr. 2:2114, 1922.

2. Albright, F.; Butler, A. M.; Hampton, A. O., and Smith, P. H.: Syndrome Characterized by Osteitis Fibrosa Disseminata, Areas of Pigmentation and Endocrine Dysfunction, with Precocious Puberty in Females: Report of 5 Cases, New England J. Med. 216:727, 1937.

3. Robson, K., and Todd, J. W.: Fibrocystic Disease of Bone with Skin Pigmentation and Endocrine Dysfunction, Lancet 1:377, 1939.

4. Dockerty, M. B.; Ghormley, R. K.; Kennedy, R. L. J., and Pugh, D. G.: Albright's Syndrome: Polyostotic Fibrous Dysplasia with Cutaneous Pigmentation in Both Sexes and Gonadal Dysfunction in Females, Arch. Int. Med. 75:357, 1945.

5. Stein, I.; Stein, R. O., and Beller, M. L.: Living Bone in Health and Disease, Philadelphia, J. B. Lippincott Company, 1955, p. 100.

6. Fraser, I.: Fragilitas Ossium Tarda, Brit. J. Surg. 22:231, 1934.

7. Summerfeldt, P., and Brown, A.: Osteodystrophia Fibrosa, Am. J. Dis. Child. 57:90, 1939.

8. Stauffer, H. M.; Arbuckle, R. K., and Aegerter, E. E.: Poliostotic Fibrous Dysplasia with Cutaneous Pigmentation and Congenital Arteriovenous Aneurysms, J. Bone & Joint Surg. 39:323, 1941.

9. Berardinelli, W.: Two Cases of Albright's Syndrome Observed in Brazil, J. Clin. Endocrinol. 10:1499, 1950.

10. McKusick, V. A.: Mechanisms in Genetic Diseases of Man, Am. J. Med. 22:676, 1957.

11. Knaggs, R. L.: Osteogenesis Imperfecta, Brit. J. Surg. 11:737, 1924.

12. Bickel, W. H.; Ghormley, R. K., and Camp, J. D.: Osteogenesis Imperfecta, Radiology 10:145, 1943.

13. Bryan, R. S.; Cain, J. C., and Lipscomb, P. R.: Hereditary Osteogenesis Imperfecta: A Mother and Son with Their Family Tree, Proc. Staff Meet. Mayo Clin. 31:475, 1956.

14. Albright, F., and Reifenstein, E. C., Jr.: The Parathyroid Glands and Metabolic Bone Disease: Selected Studies, Baltimore, Williams & Wilkins Company, 1948, p. 263.

Response of Infantile Gastroenteritis to Chloramphenicol

The Variability as Conditioned by the Spread of Resistant Strains of Serospecific Escherichia Coli O20

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The difficulties in assessing the value of chemotherapeutic agents in such a disease as infantile gastroenteritis, of varied and as yet not thoroughly understood etiology, are not unexpected. The discovery of Escherichia coli serotypes in association with outbreaks of the illness has recently had its repercussions in the interpretation of the results of therapeutic trial of a new drug in infantile gastroenteritis. This has been so in the work of Alexander et al. on streptomycin in infantile diarrhea.[1] Again, the correlation of clinical and bacteriological findings by Todd et al.[2] has thrown light on the variations in the progress of cases under chemotherapy, particularly of those receiving chloramphenicol.

In general, reports on the use of the latter antibiotic in the treatment and prophylaxis of infantile gastroenteritis have been favorable (Rogers et al.,[3] Smellie,[4] Clement et al.,[5] the M. R. C. trials,[6] and Todd et al.[7]). It is interesting to note, however, that lately reports on the emergence of, or ward cross infections with, chloramphenicol-resistant E. coli organisms have started to appear,[8,9] and, concerning infantile gastroenteritis, reports have been made by Wheeler et al.[10] on failure of the antibiotic in an outbreak of E. coli O111 and by Todd et al.[2]

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During a clinicobacteriological controlled investigation of infantile gastroenteritis and its treatment with chloramphenicol, it was noted, during the last period of the trial, that there was a marked change in the progress of the patients, particularly the chloramphenicol-treated cases, in which the relapses became very frequent and took the pattern of an outbreak. However, no significant cross infections occurred with any of the known "indicator organisms" of E. coli serogroups that were sought for. The majority of such relapses were associated with cross infections with one serospecific E. coli organism isolated locally several months previously and later identified by Ørskov as E. coli O20.[11] In the present publication the correlation of clinical and bacteriological findings, with particular reference to the latter organism, is presented, after a brief description of the clinical and bacteriological methods and results has been given (details of which are to be published elsewhere[12]).

Material and Periods of Work

The work included a series of 153 inpatient cases and 106 outpatient cases, together with 150 healthy infants as controls. The investigation covered a period of just over a year and was divided into three periods. Period I was from Aug. 1 to the end of October, 1954; Period II, from Nov. 1, 1954, to May 27, 1955, and Period III ended on Aug. 15, 1955. The research was carried out in a 15-bed open ward (Ward A) during Periods I and III and in a 6-bed similar ward (Ward B) during Period II. In the two wards the nursing technique

was not quite efficient. All patients with diarrhea aged 1 to 12 months were included, except those with very mild cases, those with dysenteric stools, and those with severe or specific parenteric infections. Cases in the third stage of marasmus and those who had received oral chemotherapy were also excluded. The outpatient case investigation was not intended for therapeutic trials but was carried out during the period of seasonal prevalence of gastroenteritis (Period III) mainly for bacteriological study. The bacteriological controls were healthy infants from the child-welfare center of the hospital in the same age group as the patients and had been free from diarrhea for the previous month; most of them were followed for two weeks after the first rectal swab investigation.

Conduct of Investigation

After the results of the first examination were recorded on a special case-sheet, notes about the clinical progress, treatment, and laboratory results were recorded and charted by the same worker, who visited the patients every weekday.

All infants were weighed on admission and then daily for the first four days and less often thereafter. An infant was considered marasmic when his weight was at least 20% less than his expected body weight after rehydration. The severity of gastroenteritis was assessed within 24 hours of admission. A case was regarded severe when it was heralded by severe nervous symptoms and/or shock, not rapidly responding to parenteral rehydration; moderate when dehydration and diarrhea were so marked as to necessitate parenteral rehydration, omission of which lead to a decline in the daily weight curve. Mild cases presented with slight or no dehydration, responding by gain in weight to oral administration of glucose-electrolyte solutions and a graded milk schedule, unless the infant was marasmic.

All cases were classified into one of six nutrition and severity groups that were planned out according to the infant's weight and the severity of gastroenteritis on admission. Successive cases in each of these groups were allocated in rotation to one of two treatment groups: the trial series receiving chloramphenicol and the control series given the usual ward treatment including succinylsulfathiazole (Sulfasuxidine) (which could not be omitted). During Period III a few infants' the requisite follow-up; arrangement was made mothers insisted on discharge before the end of for most of them to be seen as outpatients.

Rectal Swabs and Blood Samples for Bacteriological Investigation

Swabs were taken before admission to the ward, on the second day, and thereafter once weekly and on discharge. Where cross infections were prevalent, swabs were taken more frequently. Blood samples for agglutination (and in Period III for blood culture also) were taken from all inpatient cases starting with Case D18 in August, 1954, and from most outpatient cases. The samples were taken from inpatient cases on admission and then about once weekly in swab-positive cases and on discharge. Three postmortem examinations were performed.

Treatment

Rehydration was carried out in mild cases by the oral administration of a standard electrolyte-glucose solution. In several cases this was supplemented by subcutaneous infusion (often with hyaluronidase) for a few days. While adequate for cases of moderate severity, this route was expectedly a failure in severe cases; yet, because of technical difficulties, intravenous drip infusions could not be carried out as a rule. Potassium citrate was given by mouth, usually in 1 gm. daily doses, in all but the mildest cases. After an initial period of starvation, in the absence of breast milk, infants were given buttermilk powder according to a graded schedule whereby, by the eighth day of treatment, the severer normal-weight cases would be receiving 90 Cal. per kilogram of body weight daily in the form of buttermilk with 5% added sugar. Failure to tolerate the schedule at any time called for a return to clear fluids and regrading of milk. Vitamins B, D, and K and ascorbic acid were given routinely. Chloramphenicol palmitate or succinylsulfathiazole was administered for 7 to 10 days, the former in a dosage of 150 mg. of chloramphenicol per kilogram of body weight per day. No other oral chemotherapy was given. Penicillin was used to control parenteric infections in either group of cases.

Assessment of Response to Therapy

The criteria used are shown in Tables 1 and 2 and are essentially the same as those used by other workers.[1,9] Special attention was paid to relapses, whether occurring before or after complete clinical recovery. Again, they were considered as mild, moderate, or severe, according to the previous definitions of severity. Changes in the color or odor of stools, or slight transient changes in their consistency, unaccompanied by such symptoms as a rise in temperature, anorexia, vomiting, or abdominal distention, were not regarded as relapses.

Bacteriological Methods

Rectal swabs were streaked on plates of nutrient agar, blood agar, Salmonella-Shigella (SS) agar, and McConkey's agar. Enrichment on Muller-Kauffmann's medium followed by subculture on

TABLE 1.—*Comparison of Progress of Chloromphenicol-Treated (C) and Control (R) Cases in Nutrition and Severity Groups During all Three Period: of the Survey*

	Normal-Weight Cases, No.						Marasmic Cases, No.					
	Moderate		Mild		Total		Moderate		Mild		Total	
	C	R	C	R	C	R	C	R	C	R	C	R
Cases, No.	17	14	8	10	25	24	18	18	10	10	28	28
Duration of diarrhea 7 days (or less) after admission	8	5	5	4	13	9	4	2	5	4	9	6
Complete recovery from gastroenteritis in 15 days (or less) after admission	6	3	4	4	10	7	7	3	3	3	10	6
Cases not gaining or losing weight 15 days after admission	2	7	1	2	3	9	2	3	3	3	5	6
Deaths *	2	0†	0	0	2	0	0‡	2§	0	1	0	3

* Fatal cases are not included in other severity groups.
† One patient was discharged at request in bad general condition.
‡ Two patients were discharged at request in moribund condition.
§ One patient died of bronchopneumonia.

DCA or SS agar as well as on McConkey agar was done with each specimen whenever possible in order to exclude pathogens of the Salmonella and Shigella groups. Serotypes E. coli O111:B_4, O55:B_5, O26:B_6, O86:B_7, and O73[18] were sought for in the stools of all cases by using the corresponding K antisera. In addition to the mentioned serotypes, seven serologically different types of E. coli, each isolated from a sporadic case of gastroenteritis, were considered suspicious because of their agglutinability to a titer of 1:40 or above by the corresponding patient's serum. Sera were prepared with use of living suspensions of each of these seven strains and were added to the working pools of specific sera. One of the latter strains, labeled D48/11054, a strain of E. coli O20, proved to bear a significant relation to the cases of infantile gastroenteritis that were investigated, whereas the other six strains were less frequent and did not prevail in the wards and there was no index of their possible pathogenicity throughout this work. The identification of E. coli O20 from primary plate cultures was first attempted by slide agglutination,[34] with use of an OK serum prepared against a living suspension of strain E. coli D48/11054. Further serological identification involved the tube and absorption-agglutination techniques,[35] with use of both the steamed and living suspensions of slide-positive strains and serum E. coli D48/11054.

The titer for the K and O serum agglutinins to E. coli D48/11054 was determined in each of the blood samples obtained from the 28 inpatients that excreted E. coli O20. The tube-agglutination technique according to Widal was used for the test.

At the close of the work 126 strains of E. coli serogroup O20 that were isolated from 28 inpatients and from 4 outpatients were tested for their sensitivity to sulfathiazole[36] as well as to chloramphenicol (Chloromycetin).[37]

TABLE 2.—*Comparison of Progress of Chloromphenicol-Treated (C) and Control (R) Cases During Period of I (P I) and Period III (P III)*

	Normal Weight Cases, No.				Marasmic Cases, No.			
	P I		P III		P I		P III	
	C	R	C	R	C	R	C	R
Cases, No.	8	8	13	10	11	11	10	8
Duration of diarrhea 7 days (or less) after admission	6	3	4	2	6	3	1	1
Complete recovery from gastroenteritis in 15 days (or less) after admission	6	3	2	2	7	4	2	1
Cases not gaining or losing weight 15 days after admission	0	3	3	3	2	3	3	2
Cases that made a straightforward progress	4	2	2	2	4	1	1	1
Relapses, mild	1	1	9	4	2	3	7	5
Relapses, moderate	1	3	0	2	2	3	0	1
Relapses, severe	0	0	2	0	0	1	2*	0
Total relapses	2	4	11	6	4	7	9	6
Deaths following relapses †	0	0	2	0	0	1	0	0

* Discharged at request in moribund condition.
† Fatal cases are not included in other severity groups.

Clinical Findings

One case ($D113_1$) was readmitted and regarded as a new case ($D113_2$). Of the 153 inpatients, there were 85 marasmic infants. The number of cases admitted during Period III was 56, of which 30 were marasmic.

From all cases admitted, 48 were excluded,[12] which were classified into two categories: first were those that did not conform clinically or bacteriologically to "nonspecific" gastroenteritis, the majority of which were positive for Shigella or Salmonella, while the other category consisted of cases that were excluded from the final therapeutic assessment *only*. The latter included all the severe cases of primary gastroenteritis in which the all important intravenous drip therapy could not be performed.

Effects of Treatment

A comparison of the clinical data of the trial cases and the controls, which might have a bearing on the course of gastroenteritis, disclosed that the two series were reasonably comparable, not only in their initial condition but also in the number of cases receiving such additional therapy as penicillin or chlorpromazine (Largactil). This applied to the cases of the survey (all three periods) in either of the two nutrition groups. Again, a separate analysis and comparison of Periods I and III revealed that such variation as could be detected in the clinical data of the two periods was unlikely to be responsible alone for a difference in the progress of the cases.[12]

The progress of trial cases compared with the controls throughout the survey is shown in Table 1. The slight differences in the number of cases of comparable series are due partly to the exclusion of cases and partly to unavoidable errors in allocation. In general, cases of moderate severity, whether normal-weight or marasmic, showed a better response to chloramphenicol than to succinylsulfathiazole in all criteria except the mortality rate in the normal-weight (to be explained presently). In view of the small number of cases in each group, however, the only difference that was statistically significant was observed in the number of normal-weight cases that failed to gain (or actually lost) weight. Mild forms of the disease, however, did not show any appreciably superior response to chloramphenicol, probably because fewer "infective gastroenteritis" cases occurred among them than in the groups of moderate severity.

In Table 2 is illustrated an example of how variable the response to a trial drug could be from one period to the other of the same survey. For, whereas the trial cases compared favorably with the controls during Period I in both nutrition groups of infants, the ultimate results were about equal in Period III. This is correlated with the incidence and severity of relapses, which were more frequent and severer in the controls during Period I, accounting for one fatality. What happened in Period III was the reverse. Four trial patients had severe relapses; two of them (normal-weight) died in hospital and the other two that were marasmic were discharged at request in a moribund state.

Bacteriological Findings

The Fecal Flora of Gastroenteritis Cases Associated with E. Coli O20.—Inpatients: Twenty-eight infants, of a total of one hundred fifty-three cases of gastroenteritis, excreted E. coli O20 in their stools. Ten such infants were positive on admission (initial cases), while the other eighteen infants excreted E. coli O20 some time later (cross infections). A total of 205 swabs were cultured. The bacteriological findings related to these cases only are described.

(1) E. coli. One hundred thirteen swabs yielded E. coli O20. In four swabs, obtained from three different cases (Cases $D113_2$, D142, and D105), E. coli O20 was present in pure culture. In 98 other swabs E. coli O20 was associated with strains of E. coli that were serologically different from the sera we used. In the remaining 11 swabs,

from five different cases, E. coli O20 was associated with different E. coli organisms, few of which were identified by the sera we used. In two cases the association was observed in admission samples; thus Cases D137 and D149 excreted E. coli O20 as well as E. coli O73. The latter type of E. coli was very transient, since it was not demonstrated in subsequent swabs that were obtained at regular intervals thereafter, while E. coli O20 continued to be eliminated for a fortnight in Case D137 and for 11 days in Case D149. In the other three cases (Cases D122, D140, and D148) the association was observed in the stools some time after admission; Case D122 excreted E. coli O73 in the admission swab only, and while he was in hospital E. coli O20 was excreted as well. The patient died, and E. coli O20 was identified at postmortem examination in the contents of the intestine, from bronchopneumonic areas in both lungs, from the pleural exudate, and from the discharge of the ears. Case D140, an initial excretor of E. coli O20, excreted E. coli O86 nine days after admission. A few days later a rectal swab that was obtained from the patient was still positive for E. coli O20, while E. coli O86 had disappeared completely. Similar events occurred in Case D148, in which a transient cross infection with E. coli O86 occurred.

Fifty-six swabs had been obtained from the group of cross infections some time before the appearance of E. coli O20. They yielded, when cultured, several different strains of E. coli, none of which corresponded to the sera used except for E. coli O73, which was present in significant number in the admission swab that was obtained from Case D122 but disappeared subsequently.

Thirty-six swabs were obtained from 13 cases after they had recovered bacteriologically from infections with E. coli O20. Seven such infants initially had E. coli O20 infections, while the other six belonged to the group of E. coli O20 cross infected cases. Typable E. coli strains were frequently isolated; thus, three infants (Cases D148, D149, and D158) excreted E. coli O55 in their stools, and a fourth infant (Case $D113_1$), E. coli O86 after they had recovered from an initial E. coli O20 infection.

Density of growth of E. coli O20 in culture was estimated in terms of percentage of its colonies in the E. coli population growing on McConkey agar plates inoculated by the swab or an emulsion of the stools. Of the 10 initial cases 5 disclosed a profuse growth (90% to 100%); 4, a moderate growth (50% to 85%), and 1, scanty growth (less than 50%), in the admission specimen.

(2) Doubtful pathogens. There were 25 swabs, from a total of 205, that yielded, when cultured, a doubtful pathogen. They were isolated with the following frequencies:

	Swabs, No.
Paracolobactrum (late or nonlactose fermenters of E. coli)	10
Proteus mirabilis and/or Paracolobactrum, Klebsiella	8
Klebsiella (tagged with α-antigen)	5
Shigella alkalescens	1
Salmonella arizona (not proved serologically)	1

Doubtful pathogens were not excreted in significant number in the stools, and their occurrence on primary plates was comparable to intestinal transients, being detected in one swab and disappearing in consecutive ones. It is unlikely that doubtful pathogens could have played a part in E. coli O20 gastroenteritis. This opinion is corroborated by the fact that doubtful pathogens were two and one-half times less frequently isolated from E. coli O20-positive (7.07%) than from E. coli O20-negative swabs (18.47%).

(3) Specific pathogens. None of the 205 rectal swabs yielded a specific pathogen.

Outpatients: One hundred six infants suffering from gastroenteritis and attending the outpatient department were swabbed once or more in some cases. E. coli O20 was identified in four of them. The E. coli

type occurred in almost pure culture and in absence of specific as well as of doubtful pathogens.

Bacteriological controls: All 150 controls were negative except control Case C32, in which there was a profuse growth of E. coli O20 on culture; it was actually a case that was mistaken for a control (See below).

Serology of E. Coli O20 Isolated in Association with Gastroenteritis.—The serology of E. coli O20 strains that were isolated in the present survey has been dealt with in a separate communication.[18] Briefly, they possess a surface antigen of the B type of Escherichia antigens. Thus, they differ from the E. coli O20 organism included in the KKV (Kauffmann, Knipschildt, and Vahlne) scheme, which possesses an L type of K antigen. Though they form a homogeneous O group, the strains do not constitute a single serotype. So far, five different surface antigens have been identified. The present series of E. coli O20 strains could be classified into five types, each such type possessing one major antigen and different minor antigens.[18]

In passing it should be pointed out that strains of E. coli O86 reported in the present communication constituted a single serological type; they possess a B type of surface antigen that is different from antigen B_7 in E. coli $O86:B_7$.

Serum Agglutinins to E. Coli O20 (Strain D48/11054).—Infants were not uncommonly admitted with agglutinins to E. coli D48/11054 in their serum. Thus, eight E. coli O20 gastroenteritis cases (five initial and three cross infections) were admitted with their sera positive to a titer of 1:20 to 1:40.

Positive serum reactors were more frequent on discharge from hospital. Fourteen E. coli O20 cases on discharge possessed O or K agglutinins to E. coli D48/11054 to a titer of 1:80 to 1:320. A fourfold to an eightfold rise in the titer of D48/11054 agglutinins was not uncommonly observed on discharge of those cases that were serum-positive on admission.

Blood Culture.—Blood culture was done as a rule on all those samples in which the sera were used for agglutination. All blood samples were sterile.

Sensitivity to Sulfathiazole and to Chloramphenicol.—All 126 strains of E. coli O20 that were isolated from the present series of cases were uniformly resistant to sulfathiazole. Growth was profuse in all dilutions of the drug, even in those that contained as much as 20 mg. %. The results of sensitivity to chloramphenicol disclosed an abnormally high rate of resistant strains. Thus, while 106 strains (84.12%) could grow in presence of 50μg. of the drug per milliliter, only 20 strains (15.88%) were sensitive, being inhibited by a concentration of 12.5μg. or less per milliliter.

Correlation of Clinical and Bacteriological Findings

Period I was free from cross infection. During the last six weeks of Period II, four cross-infected cases with E. coli serotypes O111 and O55 were detected in the small Ward B, the epidemic coming to an end on discharge of the cases and change of the ward (to Ward A) at the commencement of Period III. It was during this latter period, however, that relapses were remarkably frequent, and an effort was made to search for any associated cross infections. The results are shown in Table 3. Among a total of 42 infants (41 admitted with gastroenteritis and 1 ward contact) in a changing population, 27 intraward cross infection incidents (in 26 infants) occurred over a period of two and one-half months. These were associated with 23 relapses and 1 initial illness in the only healthy ward-contact admitted during this Period (Case D119). There was only one moderate and one mild relapse associated with cross infections with serospecific E. coli O55 and O73, respectively, both occurring in marasmic infants. The latter serotype was recorded once in association with diarrhea in a child aged 11 years.[13] Cross infection with serospecific E. coli O86 and O20 appeared

TABLE 3.—*Cross Infections in Infants (Normal-Weight and Marasmic) During Period III* *

Chemotherapy	Negative on Admission		E. Coli O.55 on Admission		E. Coli O.20 on Admission		E. Coli O.86 or O.73 on Admission	
	C †	R †	C	R	C	R	C	R
Cases in each group before cross-infection, No.	17	13 ‡	0	1	4	4	2	1
Cross-infection incidents with E. coli O55	—	1			—	1 (1) §	—	—
Cross-infection incidents with E. coli O20	12 (12)	5 (5) ‖		—			1 (1)	—
Cross-infection incidents with E. coli O86	1 (1)	—		—	2 (1)	1 (1)	—	—
Cross-infection incidents with E. coli O73	—	1 (1)		—	—	1	—	—
Cross-infection incidents with Klebsiella a-strain	1 (1) ¶							

* Excluding Salmonella and Shigella infections (four cases) and patients who died early (five cases) or whose stay in hospital was less than one week (five cases).
† C, chloramphenicol-treated: R, controls.
‡ One infant (Case D119) was a healthy ward contact on admission.
§ Figures in parentheses indicate clinical relapses (or initial illness in Case D119) associated with cross infections.
‖ One case (Case D158) later had a cross infection with E. coli O55 also.
¶ Details of this case will be communicated later.

early in June, 1955, but a search for their original source among the previous occupants of Ward A (those present before its evacuation for Period III of the research) was fruitless. E. coli O86 was previously recorded in association with infantile gastroenteritis by Taylor and Charter,[19] though its etiological relation to the disease remained unproven. The number of cases involved with this serotype here is too small. By far the great majority of relapses, however (17 out of 23), were associated with cross infections with E. coli O20, and the rest of this report will be devoted to the latter cases.

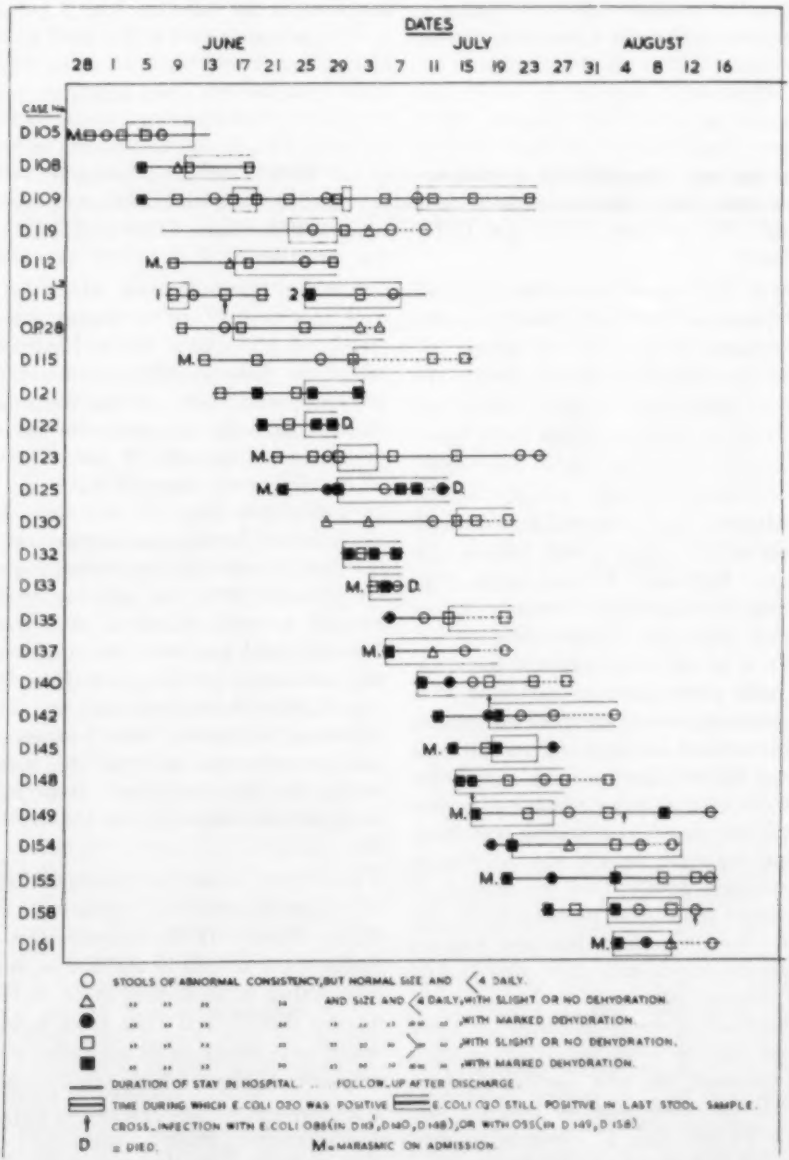
Cases Associated with E. Coli Serogroup O20.—E. coli O20 was first isolated on Oct. 7, 1954, from Case D48, a case of acute gastroenteritis of moderate severity in a 7-month-old normal-weight infant, who had chronic otitis media with a recent exacerbation. Thereafter, for several months the organism was absent from all admissions, until June 2, 1955, when it was recovered from Case D105.

Cases Whose Admission Fecal Specimens Were Positive for E. Coli O20.—Subsequently this serospecific E. coli type was recovered from the admission fecal specimens of nine cases during the rest of the work; Cases $D113_1$ and $D113_2$ were the same patient, discharged and readmitted, the organism having reappeared 15 days after the last negative swab. During the same period four outpatient cases were associated with E. coli O20. Later, on Feb. 20, 1956, it was detected accidentally in the stools of an infant (Case C32) convalescent from an attack of diarrhea two weeks before, who was mistaken for a healthy control; he was followed up and was found to develop two bouts of mild gastroenteritis in the next five weeks, with a pure growth of the serotype in each and a negative result during the intervening remission.

Of the above-mentioned 15 cases in which E. coli O20 was present in the initial fecal specimens, 8 were less than 4 months old, 5 fell in the age group 4 to 8 months, and 2 were older than 8 months. Ten were normal-weight and five marasmic, and all but three were artificially fed or mixed-fed. The initial illness was severe in 1, moderate in 12, and mild in 2. Ten of these fifteen cases were admitted. They were all dehydrated, eight severely so, their dehydration lasting from four to eight days. Three patients were admitted in varying degrees of shock. Pyrexia was present in all and was rather prolonged in six (from 4 to 14 days). Vomiting was present in all and was severe in five at the outset. All had fluid motions on admission, and the duration of diarrhea was longer than two weeks in five. Abdominal distention was present in two cases, and an enlarged liver, in one case.

Lethargy was a prominent feature in five cases.

The 10 cases happened to be distributed equally between the trial cases and the controls. In the former there were one recovery (Case D48, fifteen days after admission), two cases showing early improvement (Cases D137 and D161), and two cases showing late improvement (Cases $D113_1$ and D148). Among the controls there was one recovery (Case $D113_2$), one case improved early (Case D140), another



Cases of gastroenteritis associated with E. coli O20 on or after admission.

showed late improvement (Case D149), one deteriorated (Case D132), and one died (Case D133, the subject of bilateral hydronephrosis) (Figure). In the Figure it is also observed that in cases $D113_1$, D149, D161, and $D113_2$ E. coli O20 disappeared from the stools before discharge, and the same occurred in Case D48 (not charted). The last two cases made a complete clinical recovery coincident with the disappearance of the organisms. Cases $D113_1$, D149, and D161 made an initial improvement, which was early, remarkable, and maintained in the last but was followed by a relapse coincident with cross infection with E. coli O86 and O55 in Cases $D113_1$ and D149, respectively.

Cases of Gastroenteritis in Which E. Coli O20 Appeared in the Stools Some Time After Admission.—Among the 42 infants exposed to cross infections during Period III (Table 3), there were 9 cases positive for E. coli O20 in their admission fecal specimens, and therefore, insofar as this organism is concerned, a rough estimate of the cross infection rate during this period would be 18 out of 33 infants at risk (54.5%), a remarkably high one. As seen in the Figure, a relapse occurred on the same day as the first isolation of E. coli O20 from the stools in 9 of 17 cross infected cases admitted with gastroenteritis; in 7 cases this E. coli organism was isolated one day before the occurrence of a relapse, and in one case, two days before. Inasmuch as it was the routine to take a swab whenever a case relapsed, the chances of finding any cross infecting organism on the day of relapse were evidently greater than the chances of its isolation some time before. It is also obvious from the chart that the relapses took place in waves, each wave consisting of a few relapses occurring on the same day or at intervals of one to two days (or three days on one occasion only). Five such waves occurred, the first starting on June 16, 1955; the others were on June 26, July 13, July 19, and Aug. 2. Three of the first four waves followed a new admission of an E. coli O20 case by an interval varying from one to eight days. The fifth wave, consisting of two relapses occurring on Aug. 2, 1955, was not preceded by the admission of an E. coli O20 case within such a short interval, but it is interesting to note that these were part of relapses prevalent in the ward on Aug. 1 and Aug. 2, 1955, and associated with a ward epidemic of acute upper respiratory infection and that, apart from the two cross infections with E. coli O20, a third relapsing case showed cross infection with E. coli O55 on the same date (Case D149). In consequence of relapses in the E. coli O20 cross-infected cases two infants died (Cases D122 and D125) and the condition of four infants deteriorated.

Healthy Ward Contact Cross Infected with E. Coli O20.—This patient was a 4-month-old girl (Case D119, Figure), admitted on June 7, 1955, to Ward A in company with her mother because of shortage of beds. An admission swab was negative for serospecific E. coli. The stools of the girl were observed daily; on June 23, 1955, while they were still normal, and the baby was healthy, the culture was positive for E. coli O20 in moderate growth. On June 26, 1955, the baby suddenly developed a mild diarrhea, with marked anorexia and a low fever unaccompanied by any parenteric infection. On June 30 she was slightly dehydrated and had a little abdominal distention. She was not given any chemotherapy, and yet she improved during the next five days. Stool cultures remained positive for E. coli O20 until June 29.

Relation of Cross Infections and Relapses to Chemotherapy.—As remarked before, during Period III the relapses were more frequent and severer in the chloramphenicol-treated than in the control cases. It is noteworthy that E. coli O20 cross infections, which were shown to be associated with the majority of relapses during this period, had a predilection for the trial cases. For, of 19 chloramphenicol-treated cases, 13 were cross-infected with this serospecific E. coli

TABLE 4.—*Incidence and Severity of Relapses in the Cases That Were Cross Infected with E. Coli O20 Compared with Those in the Cases That Escaped All Cross Infections During Period III* •

	Normal-Weight Cases					Marasmic Cases				
	Cases, No.	Relapses				Cases, No.	Relapses			
		Mild	Mod.	Severe	Total		Mild	Mod.	Severe	Total
Cases cross infected with E coli O20										
Trial cases	7	6	—	1 (1) †	7 (1)	6	4	—	2 (1)	6 (1)
Controls	3	2	1	—	3	1	1	—	—	1
Total	10	8	1	1 (1)	10 (1)	7	5	—	2 (1)	7 (1)
Cases with no cross infections										
Trial cases	2	—	—	—	—	3	2	—	1	3
Controls	3	1	—	—	1	5	4	—	—	4
Total	5	1	—	—	1	8	6	—	1	7

* The total number of the latter is 13; they comprised all cases whose admission fecal specimens were positive for serospecific E. coli, except E. coli O20 initial cases (8). The latter, together with 20 other cases that were cross infected, were excluded from the 41 cases admitted with gastroenteritis in Table 3.
† Figures in parentheses indicate deaths.

type, while the corresponding figures for the controls were 15 and 5 (4 cases and 1 healthy ward-contact), respectively (Table 3). This difference in proportions is statistically significant. In order to entertain the possibility of other factors, apart from cross infections, in the production of relapses, a comparison is made in Table 4 of the incidence and severity of relapses between E. coli O20 cross-infected cases and those that were spared from all cross infections during Period III. All the 10 normal-weight cases that were cross infected relapsed, one relapse being moderate and one severe and fatal (trial case), whereas of 5 non-cross-infected cases only one had a mild relapse (while taking succinylsulfathiazole). Marasmic infants showed hardly any difference in incidence of relapses in the two groups under comparison, but there were two severe relapses following cross infection in seven cases, as compared with one in eight cases that escaped cross infection. However, it becomes clear that, in the study of relapses, it is only through a separate consideration of each of the two nutrition groups that a correlation of the former with other factors, such as therapy or prevalence of organisms in the environment, could be valuable.

Chloramphenicol Resistance in Relation to Time of Cross Infections with E Coli O20.—During the first four weeks of Period III there were five cross-infected cases in the trial series, of which two showed some sensitivity (inhibited by 12.5μg. per cubic centimeter) in their first positive fecal specimens but increased resistance in the second and third specimens. During the rest of the work all eight cross-infected cases of the trial series disclosed highly resistant strains of E. coli O20.

Comment

Relapses are a well-known feature of infantile gastroenteritis, but their cause has remained subject to discussion. In the past most emphasis was laid on the speed of regrading the feedings. Recently many workers have shown evidence of their relation to ward cross infections with E. coli serotypes (Taylor et al.,[20] Alexander et al.,[1] Wheeler et al.,[10] Anderson et al.,[21] and Todd et al.[2]). Again, relapses occurring in chloramphenicol-treated cases were attributed, among others, by El-Gholmy et al. to side-effects of the drug.[22] During the present trial minor and transient upsets related to increments in feedings were not regarded as relapses. Marasmic cases, however, presented a special problem; for, owing to the chronicity of diarrhea in most of them, their deranged digestion and metabolism, and their susceptibility to various infections, they were more prone to relapses. This has been observed

throughout the trial and is also noted in the comparison of the cases that escaped cross infections in Table 4. Nevertheless, where a separate analysis of each in Period I and Period III was made, it revealed that relapses were more frequent and severer in the controls than in the trial cases during Period I and vice versa during Period III. This applied equally to normal-weight and marasmic infants and suggests a pattern that was common to the two nutrition groups. At the same time, it became obvious from this analysis that, in general, the relapses could not have been direct side-effects of chloramphenicol. It may be noted, in passing, that according to the definitions of the severity of relapses, and of cases on admission, adopted in this work, relapses regarded as mild would fall into the category of moderate severity of other workers, e. g., Alexander et al.[1]

By correlation of the frequency of relapses during Period III with the bacteriological findings, it became evident that of 41 cases admitted with gastroenteritis, 23 relapsed after cross infections with serospecific E. coli and 8 relapsed without such incidents (Tables 3 and 4). Of the former, 17 showed cross infections with resistant strains of a serospecific E. coli O20 organism at the time of the relapse. This E. coli serogroup has not hitherto been reported in connection with infantile gastroenteritis.

It may be argued that bacteria of this group were simply chloramphenicol-resistant mutants of E. coli which developed and spread in the environment after the use of the trial drug without, however, affecting the course of infantile diarrhea and vomiting, their recovery from the stools coincidently with a relapse being merely the result of intestinal hurry produced by the latter. Nevertheless, E. coli O20 was isolated from the first fecal specimens of the 15 initial cases in a growth that was profuse in 10 and moderate in 4. Fourteen of these patients (the fifteenth being Case C32) presented with a clinical picture highly suggestive of "infective" gastroenteritis, ranging from moderate to severe in all but one; among the admitted cases either complete clinical recovery or great and early improvement occurred in the cases disclosing a simultaneous bacteriological recovery. Further, the organism was isolated from nondiarrheal stools in Cases D119 and C32 some time before the onset of clinical symptoms. Again, E. coli O20 was often recovered from the stools of cross-infected cases some 24 hours or more before the relapses of diarrhea had declared themselves. Nor was the chloramphenicol resistance of E. coli O20 likely to have been a phenomenon that was acquired during this work. For, although there is a slight suggestion of a process of successive mutations of more resistant variants in a small proportion of the cross-infected trial cases early in Period III, a high degree of drug resistance was observed in the first specimens of the majority of the initial cases. Another question which has to be considered is the lack of prevalence of E. coli O20 in the ward during Period I; it so happened that the first positive case (Case D48) was admitted at a time when there was a slackening in the rate of admissions which preceded the transfer of the patients to Ward B at the end of Period I, Case D48 having been discharged beforehand. However, it may be significant that the other initial E. coli O20 cases cropped up in June, July, and August, which is, incidentally, the seasonal prevalence of gastroenteritis in Egypt, and that, except for Case C32, the remaining 149 controls (normal infants) examined concurrently were negative for the E. coli organism in question.

Where the number of initial cases is small, however, inferences about the pathogenicity of E. coli types should be guarded. Yet, confronted with what was in fact an epidemic of relapses which could not be traced to any recognized organism during Period III, we followed the example of previous workers under similar circum-

stances, investigating the affected babies for the presence of a new type of E. coli. The relapses which were shown to be accompanied or preceded by cross infection with E. coli O20 revealed a pattern of waves that could be traced on three occasions to new E. coli O20 admissions. The correlation of these relapses and the E. coli O20 cross infections was further substantiated by a comparison of their frequency and severity with those in the cases that escaped cross infections; the difference was striking in the group of normal-weight cases.

That these cross infections with E. coli O20 were significantly more frequent in the chloramphenicol-treated than in the control cases was another salient feature of the epidemic. All strains of this serogroup were inherently resistant to sulfathiazole, and most of them were resistant to chloramphenicol. Although no records were kept of the suppressive action of these drugs on the total coliform flora, it is difficult to escape the conclusion that the predilection of cross infections for the chloramphenicol-treated cases was probably due to a more significant initial suppression of the flora produced by the antibiotic, which thus encouraged colonization of the resistant E. coli strains present in the patient's environment, as was similarly suggested by Anderson et al.[21] In this connection it is noteworthy that E. coli O73, present initially in a few E. coli O20 cases, rapidly disappeared after chemotherapy and that, whereas cross infections with E. coli O86 occurred in three initial E. coli O20 cases during chemotherapy, cross infections caused by E. coli O55 occurred after the end of therapy and, incidentally, after bacteriological recovery from a previous E. coli O20 infection. Both E. coli O73 and O55 were sensitive to the two chemotherapeutic agents used, while E. coli O86 was resistant to both. It would therefore be only through a properly conducted search for pathogenic organisms, and a continuous reassessment of their sensitivity to chemotherapeutic agents, that these agents would become of real benefit in the hospital treatment of infantile gastroenteritis, as lately remarked by Derham et al.[23]

Suggestive evidence has thus far emerged from the correlation of clinical and bacteriological results that points to the role of E. coli Serogroup O20 in the infantile gastroenteritis cases of this investigation. From the brief description of its antigenic structure, given before, it became evident that the organism in question is not endowed with an L type, but with a heterogeneous B type, of surface antigen. This feature is fully assessed in another publication (Tawil and El-Kholy[18]). It is worth while mentioning that a similar one was previously reported in connection with E. coli O25 (Cefalu et al.[24]). Two other bacteriological findings are worth commenting on. The first is the significant rise in the titer of agglutinins to E. coli O20 in the cases that were serum-positive on admission, such rise being generally considered as one of the evidences for the pathogenicity of serospecific E. coli. The second is the recovery of E. coli O20 from the pneumonic patches and other tissues at postmortem examination in Case D122; although it was possibly a postmortem invader, yet it is perhaps noteworthy that the organism was grown in pure culture.

Summary and Conclusions

An investigation was carried out on 153 inpatient and 106 outpatient infants aged 1 to 12 months, including marasmic cases, for the purpose of correlating the clinical aspects of nonspecific infantile gastroenteritis with E. coli serotypes. Controlled trials of chloramphenicol were made in the inpatients. While the trial cases compared favorably with the controls early in this investigation, the antibiotic failed in the last period. During this period relapses became very frequent in the trial cases. Cross infections with recognized E. coli types were distinctly rare. A new organism, E. coli Strain D48/11054, the somatic

antigen of which proved to belong to Serogroup O20 (in the KKV scheme), was isolated from 15 initial cases of clinically infective "gastroenteritis" of some severity, in 10 of which it was in pure culture (or almost so). It was responsible for waves of relapses in all the 17 cross infected cases, in 4 of which the relapses were moderate or severe, with 2 fatalities. In addition, a healthy infant admitted during this period was cross infected with E. coli O20 and developed gastroenteritis three days later.

The results of correlation of the clinical and the bacteriological findings, the epidemiological observations, and the serological study of the cases furnish further evidence of the probable pathogenicity of the strains of E. coli O20 encountered during this work, though the number of cases is not large. The latter organism was absent in 149 controls (healthy infants).

Cross infections with E. coli O20 (resistant to chloramphenicol) were significantly more prevalent in the trial cases than in the controls, possibly because of a stronger suppressive action produced by the antibiotic on the intestinal flora, encouraging superinfection with resistant bacteria in the environment. Hence, unless concurrent bacteriological investigation and antibiotic sensitivity tests are undertaken and are repeated according to the clinical and epidemiological events, the use of an antibiotic like chloramphenicol in gastroenteritis wards may, under such conditions as poor nursing, entail more hazard than benefit.

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REFERENCES

1. Alexander, M. B.; Benjamin, B.; Maslen, L. G. C., and Roden, A. T.: Streptomycin Treatment of Infantile Diarrhea and Vomiting, J. Hyg. 50:246-264 (June) 1952.

2. Todd, R. McL., and Hall, E. G.: The Correlation of Clinical and Bacteriological Findings in Infantile Gastroenteritis, Arch. Dis. Childhood 30: 345-353 (Aug.) 1955.

3. Rogers, K. B.; Keegler, S. J., and Gerrard, J.: Chloramphenicol in the Treatment of Infantile Gastroenteritis: Preliminary Report, Brit. M. J. 2:1501-1504 (Dec. 31) 1949.

4. Smellie, J. M.: Chloromycetin in Infantile Gastroenteritis, Proc. Roy. Soc. Med. 43:766-768 (Oct.) 1950.

5. Clement, R.; Gerbeaux, J.; Combs-Hemelle, A.; Masse, and Tetu, A.: Traitement des diarrhées graves du nourrisson par le chloramphénicol, Semaine hôp. Paris 26:3562-3565 (Sept. 10) 1950.

6. The Antibiotics Clinical Trials Committee of the M. R. C.: Antibiotic and Chemotherapeutic Agents in the Treatment of Infantile Diarrhea and Vomiting, Lancet 2:1163-1169 (Dec. 5) 1953.

7. Todd, R. McL., and Hall, E. G.: Chloramphenicol in Prophylaxis of Infantile Gastroenteritis, Brit. M. J. 1:1359-1361 (June 20) 1953.

8. Meads, M.; Harris, C. M.; Haslam, N. M., and Cline, W. A.: Chloramphenicol Fastness: Development in Vivo and Experimental Production in Vitro, J. Clin. Invest. 29:1474-1479 (Nov.) 1950.

9. Kirby, W. M. M.; Corpron, D. O., and Tanner, D. C.: Urinary Tract Infections Caused by Antibiotic-Resistant Coliform Bacilli, J. A. M. A. 162:1-4 (Sept. 1) 1956.

10. Wheeler, W. E., and Wainerman, B.: The Treatment and Prevention of Epidemic Infantile Diarrhea Associated with E. Coli O111 by the Use of Chloramphenicol and Neomycin, A. M. A. Am. J. Dis. Child. 86:350-353 (Sept.) 1953.

11. Ørskov, F., Copenhagen Serum Institute: Personal communication to the authors.

12. Aboul-Dahab, Y. W.; Shukri, H.; Tawil, G. S., and El-Kholy, S.: The Problem of Infantile Gastroenteritis in Egypt: Experiences in 259 Cases, J. Egyptian M. A., to be published.

13. Graber, C. D., and Dunlop, S. G.: Incidence of Serologic Types of Escherichia Coli Associated with Infantile Diarrhea Among Pediatric Patients in Denver Area, J. Lab. & Clin. Med. 44:416-421 (Sept.) 1954.

14. Charter, R. E., and Taylor, J.: Cultural and Serological Reactions of Strains of Bacterium Coli Isolated from Babies, J. Path. & Bact. 64:729-734 (Oct.) 1952.

15. Wright, J., and Villaneuva, R.: Differentiation of Serofermentative Types in Bacterium Coli Group 55, J. Hyg. 51:39-48 (March) 1953.

16. Harper, G. J., and Cawston, W. C.: In Vitro Determination of Sulphonamide Sensitivity of Bacteria, J. Path. & Bact. 57:59-66 (Jan.) 1945.

17. Smith, J., and Galloway, W. H.: Sensitivity to Antibiotics of Strains of Bacterium Coli Asso-

ciated with Infantile Gastroenteritis, Arch. Dis. Childhood 28:30-35 (Feb.) 1953.

18. Tawil, G. S., and El-Kholy, S.: Serological Types of E. Coli O20 in Association with Infantile Gastroenteritis, to be published.

19. Taylor, J., and Charter, R. E.: The Isolation of Serological Types of E. Coli in 2 Residential Nurseries and Their Relation to Infantile Gastroenteritis, J. Path. & Bact. 64:715-728 (Oct.) 1952.

20. Taylor, J.; Powell, B. W., and Wright, J.: Infantile Diarrhea and Vomiting: Clinical and Bacteriological Investigation, Brit. M. J. 2:117-125 (July 16) 1949.

21. Anderson, T.; Crockatt, H., and Ross, C. A. C.: A Study of Cross Infection with Type Strains of Bacterium Coli in Gastroenteritis Wards, J. Path. & Bact. 68:1-15 (July) 1954.

22. El Gholmy, A.; Abdine, Z. H., and Shukri, A. S.: Chloramphenicol in the Treatment of Infantile Gastroenteritis, Gaz. Egyptian Paediat. A. 2 and 3:406-412 (Nov.) 1954-1955.

23. Derham, R. J., and Rogerson, M. M.: Gastroenteritis in Infancy, A. M. A. J. Dis. Child. 93:113-121 (Feb.) 1957.

24. Cefalu, M., and Brancato, P., in Kauffmann, F.: Enterobacteriaceae, Ed. 2, revised, Copenhagen, Ejnar Munksgaards Forlag, 1954, p. 198.

Early Surgical Correction of Inguinal Hernias in Infancy and Childhood

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Introduction

Inguinal hernias are as old as man's attempt to meet his medical problems. However, there seems to be much cloudy thinking concerning them when they occur in infancy and childhood. Too often, inquiring parents are given the advice by their doctors that they should not worry about this situation because "it may go away," "it will recur if corrected too early," or "your child is too young to have anything done about it." Recent work has indicated that the early surgical repair of inguinal hernias is the best method of treatment.[5-7] Despite the evidence in favor of early operation and that against the use of temporizing measures, there are still many general surgeons who prefer not to attempt repair of hernias in infants. This paper reports the results of 453 inguinal herniorrhaphies in young subjects. These were done personally out of a large pediatric service in which more than 2000 cases of inguinal hernia were seen. It is our belief, based on this experience, that early surgical correction is the best treatment.

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Embryology

To understand the subject of inguinal hernias in children, one must recall a bit of the embryologic development of the inguinal and scrotal areas. At one stage in this developmental process, the inguinal canal and scrotum have no opening in them whatsoever, and it is only as the processus vaginalis passes through the internal ring, along the inguinal canal, and out the external ring to the base of the scrotum that the area is opened up for the subsequent descent of the testis (Fig. 1*A*). This processus vaginalis is nothing more than an outpouching of the peritoneum. The testis is an extraperitoneal organ and traverses the same course as the processus vaginalis to come to its final resting place in the scrotum (Fig. 1*B*). After the testis has reached its scrotal position, the processus vaginalis becomes obliterated from just above the testis back to the internal ring (Fig. 1*C*). It is estimated that the processus on the left closes about three weeks prenatally and that the right closure follows in about one week. All of these steps are complete at the time of a normal full-term child's birth.

Clinical Picture

As in adults, there are two types of inguinal hernias possible in a child—indirect and direct. The only one that is of any signifi-

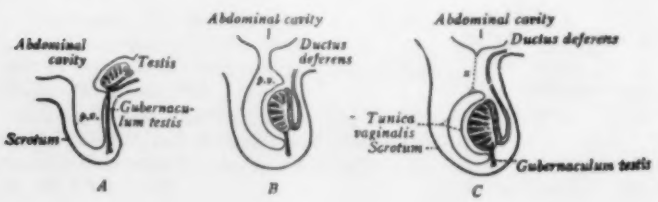

Fig. 1.—Embryology of inguinal and scrotal area.

cance is the indirect inguinal hernia, for in our series of 453 inguinal herniorrhaphies 99.6% were of the indirect variety. In the larger series of more than 2000 which came under our observation, fewer than 10 were direct hernias.

Assuming, therefore, that the indirect inguinal hernia is the problem that we face,[1,2] what is its pathogenesis? Two possibilities present themselves: 1. The processus vaginalis may never go on to complete fusion, and, therefore, the child is born with a communication between the peritoneum and the inguinal-scrotal area. This accounts for the high incidence of hernias in premature infants who have not remained in utero long enough for the obliteration to take place. 2. A closed processus vaginalis may be wedged open by an increase of intra-abdominal pressure from such causes as coughing, lifting, difficult bowel movement, or crying. Once again, a communication is reestablished between the peritoneal cavity and the inguinal-scrotal area.

Inguinal hernias are predominantly a male abnormality.[2] Four hundred ten of this series were in boys; forty-three were in girls (Table 1).

Inguinal hernias are more often seen on the right side than on the left,[3] and the incidence of bilaterality is high,[4] especially in children who are under 2 years of age. In the review of our series, we found 187 right inguinal hernias, 86 left-sided ones, and 180 bilateral hernias (Table 1). It is of interest to note that the incidence of bilateral operations is so high, because the opposite side is always opened when the physical signs make one suspicious that a contralateral hernia exists in the presence of a known unilateral one. We were led to this approach by a group of cases in which we had evidence that a one-sided hernia predisposed to the presence, or eventual occurrence, of one on the opposite side. Fifteen children who had unilateral herniorrhaphies ultimately developed a hernia on the contralateral side. We encountered 6 instances in 180 bilateral operations in which we found only a single hernia to be present when bilateral ones were suspected. In other words, this aggressive policy led to six "unnecessary" explorations. However, to offset this we had 23 other instances in which bilateral hernias were found at operation when the chief abnormality on admission appeared to be unilateral.

TABLE 1.—*Clinical Picture*

	Cases	
	No.	%
A. Sex incidence		
Males	410	91
Females	43	9
B. Side involved		
Right	187	41
Left	86	19
Bilateral	180	40
C. Age at onset		
Under 6 mo.	130	54 of follow-up

TABLE 2.—*Incarceration*

	With Incarceration
	Case No.
Emergency surgery	6
Reduction and elective surgery	18
	24

The age at the onset of symptoms or signs or both was of interest. A questionnaire was sent out to the parents of the 453 patients; of 243 replies, 130 (54%) indicated that symptoms and signs had appeared before the age of 6 months (Table 1).

Inguinal hernias have an unhappy propensity for becoming incarcerated.[5,6] Table 2 shows that 24 of the 453 hernia patients were admitted to the hospital because of an incarceration; this represents approximately 5% of the total. Sixteen (66.66%) were in infants under one year of age. Of the group of 24 admitted with incarceration, 18 had hernias which could be reduced and operated upon as an elective procedure. Six, however, needed emergency surgical correction because the incarceration could not be reduced.

Treatment

Six courses are theoretically open to one in the handling of inguinal hernias.

1. One can choose to do nothing about the hernia in the hope that it will spontaneously disappear. This is practically never successful, especially when the child is over one year of age.

2. If one is faced with a "hydrocele," there are those who advocate aspiration. This not only fails to cure the problem but may introduce simple infection or, even worse, peritonitis by aspiration of bowel contents.

3. Some persons suggest that injections of sclerosing agents at the neck of the hernial sac will bring about obliteration. This is mentioned only to condemn it because of the blind nature of the procedure. It would be exceedingly dangerous to the vascular structures and the vas deferens to undertake this method of therapy.

4. If one is faced with an incarcerated inguinal hernia, preoperative medication, elevation of the foot of the bed, and application of an ice bag to the area may prove efficacious. This does not eliminate the hernia problem but merely gives one a period for deciding when to undertake surgical correction. It is possible then to wait 36 to 48 hours after such reduction of an incarcerated hernia and do the surgery when the edema is less and the child is in better condition.

5. Some persons advocate the use of trusses. It is felt that these are of little value except perhaps to keep the lump out of view. Peritoneal to peritoneal apposition will not obliterate the hernial sac unless the surfaces are in some way scarified and roughened. Not only is a truss seldom effective, but it is actually dangerous to the cord through the pressure of the metal or hard rubber. In addition, the adhesions produced by such a truss render the surgical correction a more difficult and tedious procedure.

6. Surgical correction of the hernia is, in our opinion, the only rational and correct method of therapy for the condition. All patients in this series of hernias were treated in this fashion. The requisites for safe and effective surgery are good anesthesia administered by an anesthetist who frequently handles children, careful surgery by a surgeon experienced in the handling of cord structures in small children, and good hospital and nursing care. Having such optimal conditions under which to work, we have adopted the policy of operating on all hernias as soon as they are diagnosed after one month of age. This conforms to the feeling of other workers who also advocate early correction.[3,7]

TABLE 3.—*Age at Operation*

	Cases	
	No.	% of Total Series
Under 6 mo.	242	54
Under 5 yr.	406	90

There were two hundred forty-two of the series of 453 who were operated on when less than 6 months of age; 406, when under 5 years of age (Table 3).

Results

Recurrences are, of course, the criteria by which to judge herniorrhaphy results. Table 4 shows the follow-up on 243 cases. It was found that there were two recurrences—both immediate—one in a child under 1 year of age and one in a 7-year-old. If an acceptable recurrence rate in adults for inguinal herniorrhaphy is 5% to 10%, this 0.8% recurrence rate compares favorably. Our follow-up covered a period of from one to six years.

All parents expressed satisfaction with the scar—a skin fold, transverse type.

TABLE 4.—*Recurrences*

	Case, No.
Total follow-ups	243
Recurrences	2
Under 1 year of age	1
3-10 yr. of age	1

TABLE 5.—*Testis Size at Follow-Up*

Condition of Testis	Cases, No.
Normal and symmetrical	239
Slightly asymmetrical	4
Atrophied	0

No testis was found to be abnormally small. Table 5 shows that 239 of 243 cases followed had normal-sized and equal testes, and only 4 of the group had even slight asymmetry between the two sides.

Complications from the procedure were of three types: (1) wound infections, of which there were eight minor infections, represented in all cases by stitch abscesses; (2) "collodion burns," of which there were two. All wounds had collodion applied as the only dressing over subcuticular stitches. Two had slight blistering under the film; (3) iatrogenic cryptorchidism. Two children had normal-sized testes that were at the external ring at the time of follow-up and could not be brought down into the scrotum manually.

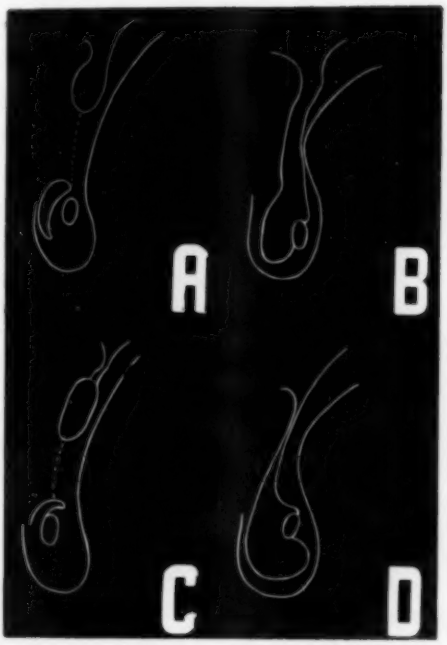

Fig. 2.—Diagrammatic representations of four cardinal presenting signs of inguinal hernia. *A*, inguinal bulge; *B*, scrotal bulge; *C*, hydrocele of cord; *D*, scrotal hydrocele.

Comment

There are four early signs of an inguinal hernia.

First.—Figure 2*A* is a diagrammatic representation of an inguinal bulge, which is frequently the first evidence that parents have that their child has a hernia. It represents a communication between the inguinal canal and the peritoneal cavity and is reproducible by getting the child to increase his intra-abdominal pressure. The bulge can be picked up by having the older child cough or strain; in one in the younger age group, crying will often bring this bulge under the examining finger.

Second.—Figure 2*B* indicates diagrammatically that the first sign of an inguinal hernia may be a scrotal bulge with fullness in the upper scrotum and inguinal canal. This is due to a persistence or reopening of the entire processus vaginalis, allowing fluid, intestines, or both to proceed down into the scrotum to produce the fullness. Once again, physical examination of such a child will give evidence of the presence of fluid or intestines in this area. This is perhaps the easiest type of hernia to diagnose.

Third.—Figure 2*C* represents, on the other hand, one of the most difficult variants of the hernia problem to be sure of. It shows a hydrocele of the cord. By this term is meant a communication between the peritoneal cavity and the inguinal canal into which some intraperitoneal fluid has passed and become sealed off at its proximal end so that the fluid does not return to the abdominal cavity. One is then presented, on physical examination, with a freely movable cystic mass in the area of the internal ring, which is difficult sometimes to distinguish from an incarcerated hernia. Points of distinction which are of help are that the mass is freely moveable and that moving it toward the pubic tubercle allows one to place his finger over a normal area of the inguinal

canal between the mass and the internal inguinal ring. It is sometimes possible in very small infants, by doing a rectal examination, to feel the internal ring from the inside and to determine whether bowel is going through the ring or not; this is corollary evidence which helps to distinguish a hydrocele of the cord from an incarcerated hernia.

Fourth.—Figure 2*D* depicts the final type of evidence which one may get of the presence of a hernia. It is sometimes called simply a hydrocele and shows itself as a full scrotum with a normal external ring and normal, nonbulging, inguinal canal. Thi , is a deceptive entity. The accumulation of fluid in the scrotum unilaterally is prima facie evidence of a communication between the hydrocele cavity and the abdominal cavity through the associated hernia. The communication is usually very small and allows fluid to pass in one direction only, oftentimes causing some confusion. In examining such a child, it is a great temptation to transilluminate such a mass and tap the fluid away, with the mistaken hope that this will cure the condition. The fluid almost always recurs, and it only then becomes evident that the child had a communicating hydrocele (hernia and hydrocele) from the beginning.

If one were to draw a conclusion from the study above, it is that patients with inguinal hernias should and can have them effectively, permanently, and safely repaired at any early age. This is the principle upon which we have worked. When confronted with an inguinal hernia in a child over one month of age, our advice to the parents has been that it should be corrected as soon thereafter as convenient. This is contrary to the feelings and expressed advice of surgeons who see children infrequently. Their reluctance to undertake early surgery is understandable, since most pediatric surgery that general surgeons perform concerns emergency problems, where conditions are less than optimal for good and easy surgery. In addition, most of the hernias that such surgeons see are incarcerated ones, in which the tissues are edematous and difficult to pick up. The operation is thereby made exceedingly tedious. Finally, most men who are opposed to early surgery use the argument that the tissues will be bigger and better at a later date. While one must admit that there is truth in this statement, it is predicated upon the point of view that a formal hernia repair is necessary to correct the problem. Actually, since over 99% of hernias seen in infancy and childhood are of the indirect variety, the cardinal point in the therapy is the separation and high ligation of the hernial sac. Most surgeons perform some type of herniorrhaphy after this ligation, but the important part of the operation is the ligation of the sac at the internal inguinal ring. This ligation can be as effectively done early as late.

We feel that, in view of the high incidence of incarceration of childhood hernias, operation should be done at an early age to prevent the grief which ensues to child, family, and pediatrician when the "watch and wait" theory is followed. Early surgery eliminates the intermittent occasions of pain, discomfort, and gastrointestinal upset for the child. The mother avoids the anxiety of wondering if the crying child is having an incarceration episode which may be dangerous. The pediatrician is spared the numerous telephone calls and constant reassurance to the mother about the situation. If such early correction were fraught with an undue risk to the future health of the testis, or if there were a high recurrence rate in this type of surgery, one would not be wise in recommending it. On the contrary, however, the results are not dangerous to the testis and the recurrence rate is less than that encountered in adult life.[3] All this seems to justify the employment of early surgical correction in the care of inguinal hernias in the pediatric group.

Summary and Conclusions

A group of 453 inguinal herniorrhaphies in infancy and childhood is reviewed from

an embryologic, clinical, and therapeutic standpoint.

It is concluded that, given safe anesthesia, experienced surgery, and good nursing care, a child should have his hernia repaired surgically at the time of diagnosis, if the child is a month of age or older.

Results in this series indicate that early surgical correction has been both safe and effective.

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REFERENCES

1. Dunavant, W. D., and Wilson, H.: Inguinal Hernias in Infants and Children, J. Pediat. 44: 558-562 (May) 1954.

2. Packard, G. B., and McLauthlin, C. H.: Treatment of Inguinal Hernia in Infancy and Childhood, Surg. Gynec. & Obst. 97:603-607 (Nov.) 1953.

3. Potts, W. J.; Riker, W. L., and Lewis, J. E.: The Treatment of Inguinal Hernia in Infants and Children, Ann. Surg. 132:566-567 (Sept.) 1950.

4. Rothenberg, R. E., and Barrett, T.: Bilateral Herniotomy in Infancy, Surgery 37:947-950 (June) 1955.

5. Clatworthy, H. W., Jr., and Thompson, A. G.: Incarcerated and Strangulated Inguinal Hernia in Infants: A Preventable Risk, J. A. M. A. 154: 123-126 (Jan. 9) 1954.

6. Rendle-Short, J., and Havard, C.: Incarcerated and Strangulated Inguinal Hernia in the First Year of Life: Report on 46 Cases, Brit. M. J. 1:680-682 (March 20) 1954.

7. Bruton, D. S., and Heaton, L. D.: The Early Correction of Inguinal Hernia, J. Pediat. 46:437-444 (April) 1955.

Editorials

THE FOREIGN LITERATURE

There is a conviction on the Continent that American bibliographies are narrow. There is prevalent a feeling that Americans care little for most of the European medical literature. In what may well appear to represent a paranoid sentiment, there is also a measure of truth. There are three reasons that help explain this fundamentally unhappy situation.

First, two world wars have hindered the development of research in medicine and surgery much more in Europe than they have in America. The economic, political and military unrest prevalent on the Continent has not existed to any such a continuous degree in our country. This has allowed our research in medicine and surgery to move ahead by leaps and bounds. The same could not occur in Europe in any similar proportion. Although much of the development of new ideas in medicine and surgery has come from Europe, still the organization, financial support and opportunity for significant advancement could not be expected to thrive in nations harrowed by economic distress, threat or actuality of military occupation.

For this reason, unlike our grandfathers in medicine who traveled to Germany, France and England in the late 19th Century for the ultimate in postgraduate medical study, we, until recently, have had our sights leveled more toward our own more impressive research and technical accomplishments at home. This has tended to contain our breadth of reading.

Second, and again unlike our grandfathers who were studying abroad, we somewhat complacently have not seen the need to learn or maintain our fluency in French, German, or Spanish to the same compelling degree. As a result, we do our reading in English; and this reading is primarily in the American literature. Too infrequently do we read even the articles from England or refer to the Dutch and Scandinavian literature, so frequently translated into our own tongue. In part the fault seems to lie in our secondary schools and colleges where the languages are not adequately encouraged. In part it lies in American complacency and satisfaction with our own accomplishments. This is not encountered to such a degree among educated Europeans, who are commonly fluent in English and refer frequently to our literature.

Third, as the study of medicine and surgery becomes more complicated and as our knowledge of these subjects increases, we must assimilate a larger mass of literature if we are to have even the barest essentials at hand. We find it difficult enough to absorb our own prolific literature. It is not often possible to add to this effort an extensive culling of the foreign literature.

To understand these difficulties is not to be resigned to them arbitrarily. There is a growing need in the postwar medical world for us to be more aware of the excellent work going on outside our country. There should be more emphasis placed upon the development of ability in languages. Our schools in some respects hold the key to this solution. An active foreign literature shelf is

absent in most of our medical libraries and those having such journals find they are little used. Our efforts should be put to the correction of these faults so that through the exchange of ideas and through international medical meetings, less duplication of effort will occur and our understanding of disease will profit.

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Case Reports

Rupture of an Angiomatous Malformation of the Pleura in a Newborn Infant

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Introduction

Congenital malformations leading to early death in infants are not uncommon. The following case presents a vascular malformation involving the pleura and interlobar fissures covering both lungs. The physiological events following birth which are related to the primary expansion of the lung and the establishment of normal respiratory gas exchange were also responsible for changes in the malformation leading to rupture, hemorrhage, and death.

Malformations of endothelial-lined channels in the lung and pleura have been reported. Many have been concealed under the diagnosis of congenital cystic disease of the lung. Others have been analyzed as congenital pulmonary cystic lymphangiectasis.[1,2] Laurence [3] has reviewed the literature and has accepted five cases as congenital pulmonary lymphangiectasis, to which he added three cases of his own. Angioma or angiomatous malformation of the lung has been reported by Schuster,[4] Orzechowski,[5] Taylor and Moore,[6] and Jaffé.[7] These have all been associated with other vascular malformations elsewhere in the body.

The case reported herewith is of an isolated pleural capillary angiomatous malformation with rupture and death due to intrapleural hemorrhages associated with atelectasis secondary to massive bilateral hemothorax.

Submitted for publication March 17, 1958.

From the Department of Pathology, District of Columbia General Hospital. Pathologist, District of Columbia General Hospital; Clinical Professor of Pathology, The George Washington University, and Adjunct Professor of Pathology, Georgetown University (Dr. Weiss); Resident in Pathology, District of Columbia General Hospital (Dr. Czeredarczuk).

Report of Case

A Negro boy was delivered at term, weighing 4440 gm. and measuring 51 cm. The mother was a 23-year-old octigravida, sextipara, who had five living children. The prepartum course, labor, and delivery were uncomplicated.

The infant was given oxygen at birth, and his respirations were established three minutes after delivery. Physical examination at birth revealed clear lungs, heart rate of 144 per minute, palpable liver and spleen, weak cry, and slight activity. His condition was satisfactory until the third day after birth, when he became restless, dehydrated, and slightly jaundiced and developed rapid respiratory movements; his temperature rose to 100.4 F. Oxygen, high humidity, antibiotics, and vitamin K were administered, without effect. The respiratory distress became progressively worse; the infant showed flaring of the alae nasae, substernal retraction, and bilateral basilar crackling rales, and he died 70 hours after birth.

Pathological Findings.—Gross: The positive findings were restricted to the respiratory system and the meninges.

Thoracic contents. Both pleural cavities were filled with unclotted and clotted blood. The hemorrhage suffused slightly into the mediastinal soft tissues.

Lungs. The lungs were dark, black-red, collapsed, acrepitant, and indurated. Sections of lung tissue failed to float in water. The visceral pleural surfaces were studded by thin-walled, cyst-like structures, measuring 0.2 to 1.2 cm. in diameter, containing blood. These were particularly prominent over the lower lobes. Several of the larger cysts were ruptured.

The pulmonary parenchyma was airless and congested. The tracheobronchial tree and major pulmonary vessels were not unusual.

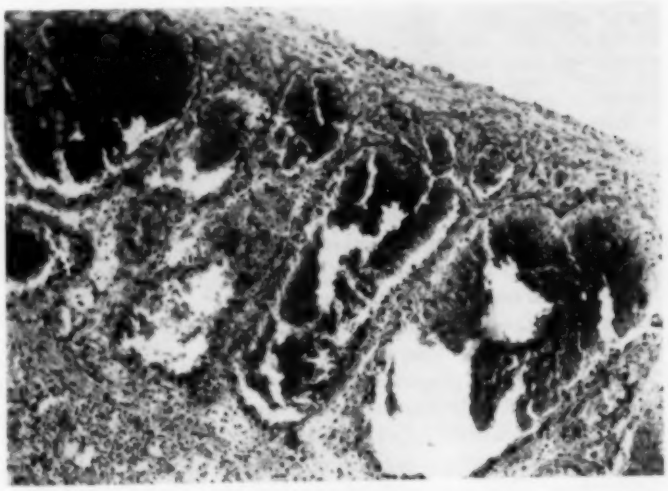

Fig. 1.—Dilated blood-containing vascular spaces within the visceral pleura. Hematoxylin and eosin; × 150.

Meninges. There was slight congestion of the pia-arachnoid. No other significant gross pathological findings were noted.

Microscopic Findings: Lung. The visceral pleural and interlobar pleural structures contain, within their connective tissues, numerous large blood-filled spaces lined by endothelial cells. The walls of these spaces consist of an endothelial layer lying on a loose connective tissue structure which contains fine fibers, rare fibroblasts, and occasional leukocytes. Stains for elastic fibers reveal none in this structure; stains for collagen reveal only a single collagen fiber coursing between adjacent spaces. Lying parallel to the mesothelial surface of the pleura, very fine elastic fibers and thin collagen fibers are present. These fibers are interposed between the mesothelium of the pleura and the underlying vascular spaces. Many of the vascular spaces rupture into one another, leaving peninsula-like remnants of the intervening wall jutting into the lumen. Several of the largest vascular spaces have ruptured their walls and the overlying pleural connective tissue and mesothelium, thereby communicating with the pleural cavities.

Rare vascular spaces have a funnel-like structure at one point consisting of an abruptly narrowed lumen reaching the size of an arteriole or venule, at which point the endothelium is surrounded by a fine thin elastic fiber mesh. These, in turn, are surrounded by a layer of collagen. Serial sections of

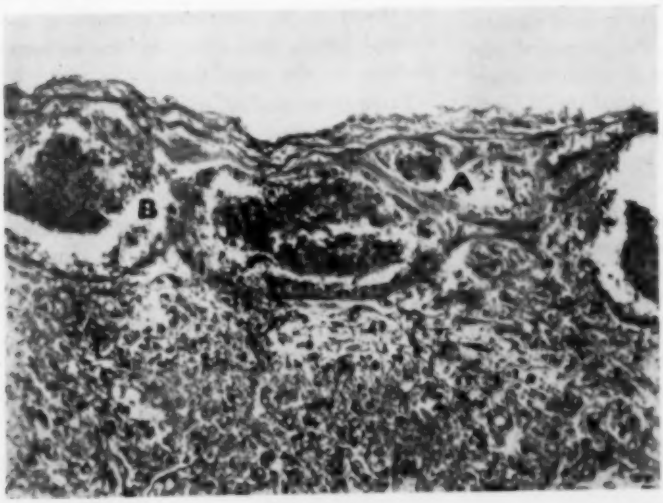

Fig. 2.—Dilated vascular channels, demonstrating the abrupt funnel-like narrowing (*A*) and the rupture of channels into one another (*B*). Weigert elastica-Van Gieson stain; × 150.

these channels suggest their communication with pulmonary veins. No communications with the arterial tree were demonstrated.

Comment

Congenital malformations may cause physiological embarrassment and may result in early death. Their usual course is associated with sudden or gradual interference with vital functions, tumorous encroachment on vital organs, or a structure or location causing the patient to become peculiarly prone to infection. The reported case describes a congenital angiomatous malformation of the visceral pleura in an infant, which underwent rupture of its cavernous formations, with consequent massive intrapleural hemorrhage. The temporal relationship of the rupture to the establishment of the pulmonothoracic dynamics of the newborn infant is suggestive of a causal relationship, as well.

At birth, the inflation of lungs is dependent upon the fetal inspiratory force of the diaphragm and of the thoracic cage with its musculature. These structures act to create a negative pressure in the potential pleural spaces. This negative pressure must equal or exceed the resistance of the lung to expansion. The resistance is based upon the tension of the elastic and muscular tissues of the pulmonary parenchyma and the cohesion of moist surfaces, or fluid-containing spaces, comprising the bronchial and alveolar system of the lung. The combined initial resistance may be equal to 20 to 30 cm. of water.[8,9] The applied negative intrapleural pressure may be of considerably greater magnitude.

The effect of the application of high negative pressure to distensible capillaries would be of the same order as the effect of that pressure applied to distensible pulmonary alveoli. The small existing lumina would rapidly increase in size, and inrushing blood would maintain the new diameters. In areas in which there is no protection of the capillary wall by a cushion of soft tissues, the wall may rupture. It is believed that this was the mechanism of rupture of the pleural angiomatous malformation.

The influence of systemic blood pressure changes is believed to be negligible. The capillary bed of the pleura is derived from the bronchial arterial system; hence, this group of vessels should follow the same cardiovascular dynamic changes seen in other parts of the systemic circulation. Any difference must be ascribed to local intrathoracic factors and to abnormalities of the vessel walls. Since the increase in systemic blood pressure is gradual, starting in the prenatal period, the larger changes in intrathoracic pressure probably play the dominant role.

Anatomical studies of the vascular channels and their walls confirm the capillary nature of their structure. Most of the dilated vessels are composed of intima, lying on loose connective tissue. The capillary angiomatous spaces communicate with vessels having a narrow coat of fine elastic fibers surrounded by a layer of collagen. The communications between these two types of vessels do not appear to be at branchings but rather are an abrupt change of diameter of the lumen, with equally abrupt change in the elastic fiber structure of the wall.

There is no appreciable difference between the vessels in the interlobar portions of the visceral pleura and those in the external portions of the same layer.

From these studies, it is believed that the vascular structure seen in the visceral pleura is a capillary angiomatous malformation which probably communicates with the pulmonary venous system. The application of sudden negative pressure to this structure resulted in distention of the capillary lumina into a cavernous formation and rupture of the thinned, stretched walls of many of the enlarged vessels into one another. In some instances this was associated with rupture of the overlying thin pleura, resulting in open bleeding channels into the pleural spaces.

Conclusion and Summary

A case of capillary angiomatous malformation of the pleura is presented. The sudden application of negative intrapleural pressure at birth is believed to have caused rapid distention of the unprotected vascular channels, with subsequent rupture and massive bilateral hemothorax.

Mr. Julius Weber did the photographic work.

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REFERENCES

1. Virchow, R.: Gesammelte Abhandlungen zur wissenschaftlichen Medicin, Frankfurt, Meidinger Sohn u. Comp., 1856, p. 982.

2. Klebs, E.: Die allgemeine Pathologie, Jena, G. Fischer, 1889, Vol. 2, p. 335.

3. Laurence, K. M.: Congenital Pulmonary Cystic Lymphangiectasis, J. Path. & Bact. 70:325-333, 1955.

4. Schuster, N. H.: Familial Haemorrhagic Telangiectasia Associated with Multiple Aneurysms of the Splenic Artery, J. Path. & Bact. 44:29-39, 1937.

5. Orzechowski, G.: Über die primären blutbildenden Hemangioendotheliome der Leber, Arch. path. Anat. 267:63-72, 1928.

6. Taylor, A. C., and Moore, E.: Multiple Hemangiomas Showing Certain Malignant Characteristics in an Infant, Am. J. Cancer 19:31-39, 1933.

7. Jaffé, R. H.: Multiple Hemangiomas of the Skin and of the Internal Organs, Arch. Path. 7: 44-54, 1929.

8. Smith, C. A., and Chisholm, T. C.: Intrapulmonary Pressures in the Newborn Infant, J. Pediat. 20:338-346, 1942.

9. Wilson, J. L., and Farber, S.: Pathogenesis of Atelectasis of the New-Born, Am. J. Dis. Child. 46:590, 1933.

Simple Renal Cyst in Children

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We are adding 1 more case of simple renal cyst to the 21 recorded cases in children as reported by DeWeerd and Simon.[1] In an excellent review of this condition, they emphasized the congenital nature of the lesion. There are no further reports in the English literature to date.

Report of Case

A 2¼-year-old white boy was first admitted to the hospital on Sept. 4, 1956. One month prior to admission his mother noticed a large swelling involving the left upper quadrant of the abdomen. Physical examination confirmed this finding, and he was admitted for investigation. The past and family histories were noncontributory.

Examination at admission revealed a fixed nontender smooth mass occupying the left upper quadrant and left flank. The rest of the examination was essentially negative except for a small umbilical hernia.

Laboratory data were as follows: hemoglobin, 14 gm.; erythrocytes, 4,160,000 per cubic millimeter; leukocytes, 6700 per cubic millimeter, with a differential count of 60% polymorphonuclear cells, including 7% stab cells, 38% lymphocytes, and 1% monocytes. The urine was yellow, cloudy, and alkaline, with specific gravity of 1.022, and it was negative for sugar and albumin. Urinary smear revealed occasional erythrocytes and epithelial cells.

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Fig. 1.—Intravenous pyelogram and urogram reveal a large opaque mass occupying the left upper and midabdominal regions. The left upper renal collecting system is compressed, grossly distorted, and displaced medially and inferiorly.

Intravenous pyelogram and urogram revealed a rather large soft tissue mass occupying the left upper and left midabdominal regions with definite bulging of the flank. The left upper renal collecting system was compressed, grossly distorted, and displaced medially and inferiorly by this soft tissue mass (Fig. 1). The tumor mass measured 9.5 by 12.0 cm. in diameter on the anteroposterior film.

Temperature and pulse were never elevated. Three days after admission exploratory laparotomy was with use of ethylvinyl ether (Vinamar), ether, and oxygen anesthesia.

The preoperative diagnosis was renal embryoma (Wilms' tumor). The history, physical examination, x-rays, and laboratory findings were classically consistent with this impression.

At laparotomy, the left kidney presented as a cystic mass measuring 20 by 10 by 10 cm. The right kidney was normal in size and position. The liver was also normal. Further abdominal exploration revealed no other pathology. The left kidney and cyst were easily shelled out en masse. The postoperative course was excellent, and the patient was discharged three days later, on Sept. 10, 1956. Up to the date of writing the boy has made an uneventful recovery and growth and development are normal.

The pathological examination was done by Dr. Clarence I. Owen, pathologist of Grace Hospital, Detroit. His report is as follows: On gross examination the specimen was found to be a kidney in which a cyst was present. The entire specimen weighed 540 gm. and measured 13 by 10 by 10 cm. The kidney tissue at one end measured 3 by 3½ by 4 cm. This appeared normal except adjacent to the cyst, where it was markedly compressed. The kidney contained a compressed pelvis. The cyst did not communicate with the pelvis and measured approximately 10 cm. in diameter. The wall ranged from 1 to 3 mm. in thickness. The lining was smooth. The lumen was filled with clear straw-colored fluid. On microscopic examination, the kidney tissue apart from the cyst exhibited

Fig. 2.—Microscopic section demonstrates thick hyaline cyst wall and severe distortion and compression of adjacent normal renal parenchyma.

no pathology. The pelvic structures were normal. The cyst had a wall made up of hyaline connective tissue, and it was lined by a single layer of flat cells. No malignancy was present (Fig. 2).

Comment

Our case satisfied the following criteria as proposed by DeWeerd and Simon:

1. The cyst was unilocular.
2. There was no communication between the cavity of the cyst and the renal pelvis.
3. The cavity of the cyst was lined with epithelium.
4. No renal elements were contained within the cyst wall.
5. A localized region of the kidney was involved.
6. The uninvolved renal tissue was relatively normal, grossly and microscopically.
7. The renal pelvis and ureters were patent.

In simple renal cyst, the operation of choice would be excision of the cyst wall. In most cases, however, the extensive destruction of the renal parenchyma necessitates nephrectomy. Clinical differentiation of this condition from Wilms' tumor is almost impossible. As in our case, three out of four simple renal cysts are found in males on the left side.

Summary

The 22d case of congenital simple renal cyst in children is presented. This case fulfilled the seven criteria proposed by DeWeerd and Simon.

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REFERENCES

1. DeWeerd, J. H., and Simon, H. B.: Simple Renal Cysts in Children: Review of the Literature and Report of 5 Cases, J. Urol. 75:912-921 (June) 1956.

Idiopathic Hypercalcemia of Infancy

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The disease called "idiopathic hypercalcemia of infancy" has received considerable attention in recent European pediatric literature. Butler [1] and Fanconi [2,3] reported the first two cases in 1951. In 1953 the syndrome was first clearly delineated by Lightwood and Stapleton.[4] Since then, many cases have been seen in Great Britain,[5-12] where, in fact, the condition appears to be comparatively common. It is reported that in Dundee, Scotland, 5% of all babies entering hospitals between the ages of 6 and 12 months were found to have this disorder.[8]

By contrast, the disease has been almost unknown in the United States. To date only five cases have been reported in this country.[13-15] Doubtless, however, there have been more cases that have been unrecognized, and it behooves the American pediatrician to acquaint himself with the clinical features of the disease. This is especially true because early diagnosis and treatment may be essential to prevent permanent cerebral damage.

The following appears to be the sixth case of this disease reported in the United States.

Report of Case

The patient, the first offspring of healthy parents, weighed 5 lb. 6½ oz. at his birth, Jan. 10, 1956. On his first visit to the Ochsner Clinic, at the age of 2 months, he weighed 8 lb. 7 oz. and, on careful examination, appeared to be a normal, healthy, vigorous infant. Because of mild constipation his diet was changed from evaporated milk to a low-calcium formula (Similac).

Nevertheless, constipation persisted and he became a rather fussy baby. His mother did not consider him ill, however, until the age of 6 months, when he began having persistent fever, his rectal temperature rising to 101 or 102 F each day. On examination at this time a loud systolic murmur was heard over the whole precordium. Since the murmur had previously been absent, endocarditis was suspected, and the child was admitted to the hospital. During his stay of one week in the air-conditioned ward the fever subsided, and repeated blood cultures were sterile. The blood pressure was 120 mm. Hg systolic and 60 to 70 mm. Hg diastolic. No abnormalities were detected in roentgenograms of the chest or in the electrocardiogram. The blood urea nitrogen level was 23 mg/100 ml.

The child was discharged with a tentative diagnosis of congenital heart disease. The previous fever was thought to be due to environmental warmth, and the parents were advised to protect the child as much as possible from the excessive heat of summer.

Thereafter the baby continued free of fever but otherwise failed to improve. He remained fretful and constipated, took his feedings poorly, and seemed to stop growing physically and mentally. Figure 1 illustrates graphically the cessation of growth in weight beginning at the age of 6 months.

At 7 months of age the baby was readmitted for further study. By this time he seemed clearly

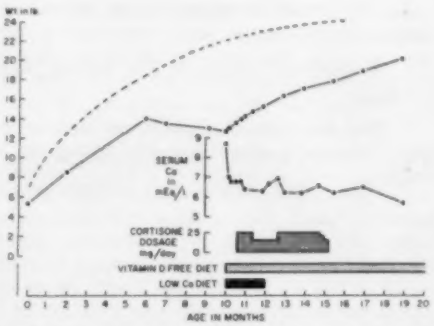

Fig. 1.—Graphic illustration of patient's growth in weight compared with the average normal boy (represented by broken line). Note growth failure beginning at the age of 6 months, with resumption of gain in weight on institution of treatment at 10 months of age. Growth in height followed a parallel curve, with cessation of growth between 6 and 10 months of age. Changes in serum calcium levels correlated with dietary and steroid therapy are shown in the smaller graph.

Submitted for publication March 13, 1958.

From the Department of Pediatrics, Ochsner Clinic and Ochsner Foundation Hospital.

Fig. 2.—"Elfin" appearance of patient, as seen at the age of 10 months, when treatment was started. Note sad appearance with hanging jowls and full lips.

retarded in development. He made no attempt to sit alone. Although he could grasp objects, he did not carry them to the mouth. Systolic blood pressure varied from 140 to 180 mm. Hg while he was awake, but under narcosis induced by rectal administration of thiopental sodium it was only 100 mm. Hg systolic and 60 mm. Hg diastolic. Because of a history suggesting excessive thirst (he took 24 to 32 oz. of milk plus 12 oz. of water daily), attention was focused on renal function. Results of urinalysis on four occasions were normal, but the highest specific gravity was 1.011. The blood urea nitrogen level was 16 mg/100 ml.; serum sodium, 145.1 mEq. per liter; potassium, 4.1 mEq. per liter; chloride, 104.1 mEq. per liter, and bicarbonate, 24 mEq. per liter. No abnormalities were detected in the intravenous urogram or electroencephalogram. Concentrations of sodium and chloride in the sweat were 17.5 and 20.4 mEq. per liter, respectively. After fluids had been withheld for 12 hours in an attempt to test the renal electrolyte-concentrating power, no adequate specimen of urine could be obtained. Our suspicion of renal diabetes insipidus therefore could not be confirmed.

The last admission to the hospital was in November, 1956, when the baby was 10 months old. He still weighed only 13 lb., seemed malnourished, had loose skin hanging in folds, and presented a peculiar facies with hanging jowls and prominent lips (Fig. 2). Further studies were made. The blood urea nitrogen level was 22 mg/100 ml. The serum sodium, potassium, chloride, and bicarbonate levels were still normal. Total serum protein was 5.7 gm/100 ml., with albumin 3.7 gm. and globulin 2.0 gm/100 ml. Results of tests of thyroid function included a normal protein-bound iodine level (5.4μg/100 ml.) but elevated serum cholesterol (443 mg/100 ml.).

It was at this time that my attention was called to the publication of Lightwood and Stapleton[4] on infantile hypercalcemia. The clinical features of this case, and even the hypercholesteremia, seemed to fit their description. For the first time, the calcium metabolism was examined; the serum calcium level was 8.7 mEq. per liter (17.4 mg/100 ml.); phosphorus, 6.4 mg/100 ml., and phosphatase, 4.1 Bodansky units. Sulkowitz tests of the urine indicated only a trace to 1+ reaction for calcium. Heavy lines were demonstrated roentgenographically at the metaphyses of the long bones, along the iliac crest, and around the bodies of the vertebrae (Fig. 3). In the absence of any other evident cause for hypercalcemia, and because of the close clinical resemblance of this case to those of the British authors, a diagnosis of idiopathic infantile hypercalcemia was made. It should be noted that the child had never received unusually large amounts of vitamin D. He had always taken 0.6 cc. of a vitamin preparation (Tri-Vi-Sol) daily, providing 1000 units of vitamin D, and a milk formula containing 400 international units of vitamin D per quart. His daily dietary calcium intake had been in the vicinity of 1 gm., since the relatively low calcium formula had been given for only a month and at other times he had been fed various formulas resembling whole cow's milk in their content of calcium.

Treatment was begun by withholding vitamin D and, as far as possible, calcium from the diet. Milk was interdicted, being replaced by a mixture of pureed beef, peanut oil, apple juice, and corn syrup. The child seemed to take this more willingly than milk and began to gain weight. After three weeks he had gained 1 lb. and his serum calcium level had fallen to 6.8 mEq. per liter (13.6 mg/100 ml.). At this time the child was given 25 mg. of cortisone a day in divided doses. Figure 1 shows the definite improvement in growth which became evident as soon as serum calcium levels were reduced in response to the diet, even before administration of cortisone was begun. Further reduction of the serum calcium level occurred coincident with the beginning of steroid therapy, but this was only a minor change and in spite of cortisone the serum calcium level remained above normal. After two months milk without vitamin D was again permitted and the

Fig. 3.—Roentgenogram taken when the child was 10 months old shows hypermineralization of bones, forming dense rings around vertebral bodies and concentric arcs of density over iliac crests. Growing ends of long bones showed dense lines at metaphyses, similar to those seen in heavy-metal poisoning.

cortisone dosage was reduced. A slight relapse occurred, the serum calcium level rising to 6.9 mEq. per liter (13.8 mg/100 ml.), but increase in the cortisone dosage again corrected the condition. However, not until the baby was 18 months old was a nearly normal calcium level (5.68 mEq. per liter) achieved. At this time he weighed 20 lb. seemed strong and happy, and ate and slept well. His heart murmur could no longer be heard, but he still had hanging jowls and protruding lips. He walked only with support. Despite the child's evident improvement, there seems reason to fear that he may ultimately be slightly deficient in intellect.

Comment

This case is typical of the severe form of idiopathic hypercalcemia of infancy, as described in the British literature. The child presented the classic "elfin appearance," with hanging jowls and thickened upper lip. The anorexia, constipation, loss of weight, and growth failure, developing at or before the sixth month of life, are typical. The impairment of mental development is also usual. The heart murmur, developing as the disease progressed and disappearing as the child improved, is a common feature. The blood pressure, often found to be elevated in this disease, is difficult to evaluate, since these children are too cross to cooperate well. This patient had hypertension when crying, but when he was put to sleep his blood pressure was normal.

Hypercalcemia, of course, is essential for the diagnosis. Phosphate and phosphatase levels in the blood do not seem to be disturbed by the disease, but hypercholesteremia, as seen in this case, has been the usual finding and tends to parallel the hypercalcemia. Azotemia, not present in this patient, is a feature of only the severest cases.

The roentgenographic findings, indicative of hypermineralization at the sites of formation of new bone, are typical. Osteopetrosis of the skull was not seen in this case, but the dense lines at the ends of the long bones, around the bodies of the vertebrae, and along the crests of the ilia are classic.

It has been suggested that there are two varieties of infantile hypercalcemia, a benign form and a severe one. Only the severe form, it is said, causes the peculiar facies, heart murmur, renal insufficiency, and mental impairment. More recently, cases of intermediate severity have been seen, and it seems likely that all cases represent the same disease, varying only in degree.

The prognosis in typical cases of the "severe form" is poor. Death may occur in renal failure with azotemia. Those patients who survive are usually mentally retarded. An important question, not yet conclusively answered, is whether hypercalcemia damages the brain or whether perhaps both the hypercalcemia and the mental impairment may represent separate expressions of a more subtle underlying metabolic disturbance, which itself may be congenital or genetic in origin. In the latter case our efforts to control the hypercalcemia may succeed in sparing the kidneys but fail to protect the brain.

As to etiology, nothing certain is known. Excessive dietary calcium may be a factor, since nearly all cases have occurred in babies taking cow's-milk formula rather than human milk. Reduction in calcium intake has therapeutic value, but whether low-calcium diets could prevent the disease is doubtful. Morgan and associates [8] reported the case of a child who had been entirely breast-fed up to the age of 8 months, when the diagnosis of infantile hypercalcemia was made. The only cow's milk this child had received was small amounts used in preparing his cereal feedings.

Vitamin D intoxication cannot in itself explain the disease, since none of the cases of patients reported in the literature received vitamin D in doses greater than those usually well tolerated. In three of the cases reported by Forfar and co-authors [10] the children had received less than 600 units of vitamin D daily. The possibility of individual hypersensitivity to vitamin D has been suggested. However, the only direct evidence we have tends to refute this hypothesis, since Forfar and associates [10] failed to induce relapse when they gave large doses of calciferol (vitamin D_2) to three patients during convalescence, after favorable response to therapy with a diet low in calcium and vitamin D.

Parathyroid disease has been ruled out by the finding at necropsy of normal-appearing parathyroid glands, by the osteopetrosis that these patients show in contrast to the tendency for demineralization in hyperparathyroidism, and by the favorable response to administration of cortisone, not seen in true hyperparathyroidism.

An attractive hypothesis, submitted by Forfar and associates,[10] correlates the hypercholesteremia with the hypercalcemia. These authors presuppose an abnormal sterol, synthesized by the body, which is measured as cholesterol by the usual laboratory methods but which has a physiologic effect similar to that of vitamin D, enhancing calcium absorption from the intestine. So far this hypothesis has not been tested.

Treatment consists in reduction of calcium and vitamin D intake and is uniformly successful in correcting the hypercalcemia. Unfortunately, by the time the diagnosis is made many patients have suffered irreversible damage to the kidneys and brain. Hence, it is important for the pediatrician or general practitioner to have a "high index of suspicion" in order that the diagnosis may be made in the early stages of the disease.

Cortisone is also effective in lowering the serum calcium level and should be used in severe cases. The mode of action of cortisone is obscure, but empirically it has been shown that cortisone corrects hypercalcemia in all conditions in which it occurs, except in hyperparathyroidism.[16]

Treatment with edathamil has been tried, but the drug has not been well tolerated.[8] Treatment with sodium phytate, effective in other forms of hypercalcemia,[17,18] deserves a trial in this disease.

Summary

A case of idiopathic infantile hypercalcemia, the sixth to be reported in the United States, is presented. Treatment with a diet low in calcium and vitamin D corrected the hypercalcemia, but some degree of permanent mental impairment is feared.

All babies who manifest unexplained impairment of appetite, growth, and development, during the first year of life, should be suspected of having hypercalcemia. A peculiar "elfin" facies, a heart murmur, and sometimes hypertension should strengthen

this suspicion. Determination of the serum calcium level will settle the question. It is hoped that by early diagnosis and treatment permanent damage to kidneys and brain can be averted.

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REFERENCES

1. Butler, N. R.: Generalized Retardation, with Renal Impairment, Hypercalcemia, and Osteosclerosis of the Skull, Proc. Roy. Soc. Med. 44:296-297 (April) 1951.

2. Fanconi, G.: Über chronische Störungen des Calcium- und Phosphatstoffwechsels im Kindesalter, Schweiz. med. Wchnschr. 81:908-913 (Sept. 22) 1951.

3. Fanconi, G.: Chronische Hypercalcämie, kombiniert mit Osteosklerose, Hyperazotämie, Minderwuchs, und Kongenitalen Misabildungen, Helvet. paediat. acta 7:314-349 (Aug.) 1952.

4. Lightwood, R., and Stapleton, T.: Idiopathic Hypercalcemia in Infants, Lancet 2:255-256 (Aug. 1) 1953.

5. Creevy, R. D. G., and Neill, D. W.: Idiopathic Hypercalcemia in Infants with Failure to Thrive, Lancet 2:110-114 (July 17) 1954.

6. Dawson, I. M. P.; Craig, W. S., and Perera, F. J. C.: Idiopathic Hypercalcemia in an Infant, Arch. Dis. Childhood 29:475-482 (Dec.) 1954.

7. Schlesinger, B. E.; Butler, N. R., and Black, J. A.: Severe Type of Infantile Hypercalcemia, Brit. M. J. 1:127-134 (Jan. 21) 1956.

8. Morgan, H. G.; Mitchell, R. G.; Stowers, J. M., and Thomson, J.: Metabolic Studies on 2 Infants with Idiopathic Hypercalcaemia, Lancet 1:925-931 (June 16) 1956.

9. Stapleton, T.; MacDonald, W. B., and Lightwood, R.: The Management of Idiopathic Hypercalcemia in Infancy, Lancet 1:932-934 (June 16) 1956.

10. Forfar, J. O.; Balf, C. L.; Maxwell, G. M., and Tompsett, S. L.: Idiopathic Hypercalcemia of Infancy: Clinical and Metabolic Studies with Special Reference to the Aetiological Role of Vitamin D, Lancet 1:981-988 (June 23) 1956.

11. Rhaney, K., and Mitchell, R. G.: Idiopathic Hypercalcemia of Infants, Lancet 1:1028-1032 (June 30) 1956.

12. Idiopathic Hypercalcemia in Infancy, Editorials, Lancet 1:1052-1053 (June 30) 1956.

13. Daeschner, G. L., and Daeschner, C. W.: Severe Idiopathic Hypercalcemia of Infancy, Pediatrics 19:362-371 (March) 1957.

14. Clinical Pathological Conference, J. Pediat. 51:461-473 (Oct.) 1957.

15. Bongiovanni, A. M.; Eberlein, W. R., and Jones, I. T.: Idiopathic Hypercalcemia of Infancy, with Failure to Thrive, New England J. Med. 257:951-958 (Nov. 14) 1957.

16. Connor, T. B., et al.: Use of Cortisone and ACTH in Hypercalcemic States, J. Clin. Endocrinol. 16:945 (July) 1956.

17. Vagelos, P. R., and Henneman, P. H.: Effect of Sodium Phytate on the Hypercalcemia of Acute Quadriplegia Due to Poliomyelitis, New England J. Med. 256:773-776 (April 25) 1956.

18. Cogan, D. C., and Henneman, P. H.: Diffuse Calcification of the Cornea in Hypercalcemia, New England J. Med. 257:451-453 (Sept. 5) 1957.

Progress in Pediatrics

The Ostium Primum Syndrome

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Prior to the development of intracardiac surgery the group of congenital anomalies associated with persistence of the ostium primum, although known to pathologists, was not clearly separated from other types of septal defect in the minds of clinicians. However, their physiologic and surgical implications are of great importance.[1,2] Bailey et al. have reported postoperative death in 11 of 16 patients with the ostium primum type of atrial septal defect but in only 3 of 30 with other types, such as ostium secundum. The purposes of this paper are to review the descriptive literature, to suggest a possible relationship and a scheme of classification of these various entities, to emphasize a reason for the high operative mortality, and to point out clinical features of diagnostic significance.

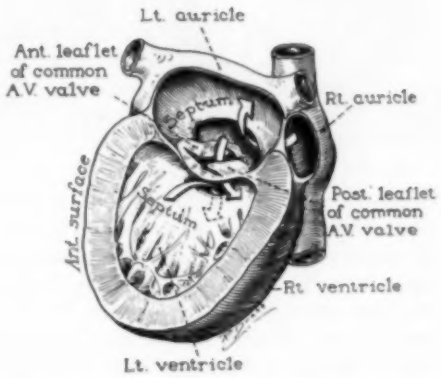

Fig. 1.—Semidiagrammatic representation of AV canal. Arrows pass through ostium primum, common AV orifice, and interventricular defect but do not necessarily indicate direction of flow. (Reproduced with permission from Rogers and Edwards,[9] *American Heart Journal*, The C. V. Mosby Company.)

Pathology

Persistent common atrioventricular canal is probably the most familiar complex associated with ostium primum. There are four features.

First, there is a defect (ostium primum) in the lowest part of the interatrial septum immediately above the atrioventricular valves. The inferior margin of the septum is free, as shown in Figure 1, and arches across the plane of the atrioventricular valves in such a manner as to suggest that it never became attached to the underlying structures. Higher in the septum is the foramen ovale, which may be closed or functionally or anatomically open but in any case has no particular connection with the defects under consideration.

Second, the interventricular septum is defective in that its posterior portion fails to extend up to the normal plane of the atrioventricular valves and a pars membranacea is lacking. The remaining septum is low posteriorly and has a free concave muscular crest under the atrioventricular valves. The valves are loosely attached to it by chordae tendineae so that flow of blood between the ventricles is permitted. Anteriorly the margin of the crest curves upward to form the posterior edge of the

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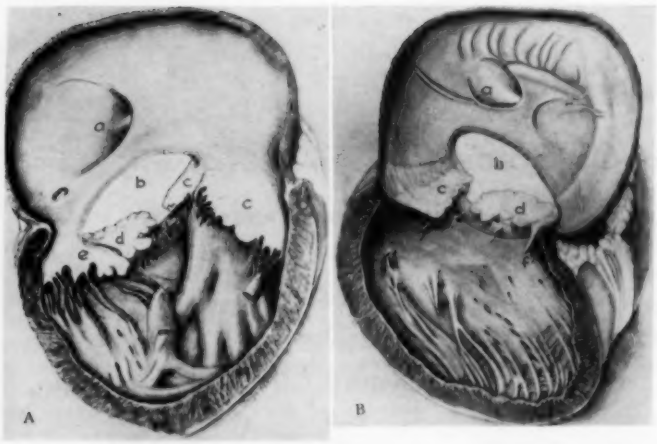

Fig. 2.—AV canal, dissected specimen. Edges of incisions in ventricular and atrial walls have been widely retracted. *A*, right side; *B*, left side. (*a*) Foramen ovale; (*b*) ostium primum; (*c*) anterior common leaflet; (*d*) posterior common leaflet; (*e*) posterior tricuspid leaflet; (*f*) part of posterior mitral leaflet.

relatively normal anterior portion of the septum which divides the outflow tracts of the ventricles. The combined interatrial and interventricular openings thus appear to be one large hole bounded superiorly by the free concave margin of the atrial septum and inferiorly and anteriorly by the free concave margin of the ventricular septum.

Third, the aortic (septal, anterior) cusp of the mitral valve is cleft from base to apex, and so there are two completely separate halves.

Fourth, the septal cusp of the tricuspid valve is cleft in the same manner. Furthermore, the posterior half of the cleft mitral leaflet and the posterior half of the cleft tricuspid leaflet are fused above the interventricular septum, forming a long posterior common leaflet which passes through the septal defects and is attached by chordae tendineae at its left end to papillary muscles in the left ventricle and at its right end to papillary muscles in the right ventricle. Likewise, the anterior halves of the two cleft leaflets are fused to form an anterior common leaflet which also passes over the interventricular septum through the defects and is similarly attached to chordae tendineae in both ventricles. The anterior and posterior common leaflets are also attached at their midportions by chordae to the underlying crest of the ventricular septum. Owing to the concavity of the latter, the two common leaflets lie somewhat deeper below the atrioventricular groove than their component parts normally would. This position can be seen in the two parts of Figure 2. The size of the interventricular passageway varies greatly from specimen to specimen, depending on the length of the chordae connecting the valve leaflets to the crest of the septum. When they are very short the interventricular passage has little or no patency, but when they are long it is widely open. In Figure 3, "A-V canal," the atrioventricular valves may be seen from the atrial aspect. It will be noted that, owing to the abnormalities just enumerated, there is no division of the passage from atria to ventricles into right and left sides but that there is only a single atrioventricular

Fig. 3.—Valve arrangement in ostium primum defects. Diagram showing arrangement of the atrioventricular valves as seen from the atrial surface. See text. (*1*) Posterior cusp of mitral valve; (*2*) aortic cusp of mitral valve; (*3*) septal cusp of tricuspid valve; (*4*) anterior cusp of tricuspid valve; (*5*) posterior cusp of tricuspid valve.

orifice (common atrioventricular canal). It is usually guarded by five valve leaflets: the relatively normal posterior cusp of the mitral valve (*1*), the abnormal anterior common leaflet (*2a-3a*), the relatively normal anterior tricuspid leaflet (*4*), the relatively normal posterior tricuspid leaflet (*5*), and the abnormal posterior common leaflet (*2a-3b*). Reference to Figure 3, "Normal," should make it apparent how the valve arrangement in AV canal is related to the normal arrangement. The presence of clefts along the dotted lines and absence of the septa in the neighborhood of the atrioventricular valves would convert the latter to the former. Other abnormalities of any of the atrioventricular leaflets, such as nodularity, thickening, perforation, adhesion to the ventricular wall, and shrinkage, have been described frequently. The foregoing description is based on that of Rogers and Edwards[3] supplemented by observations on our own cases.

Although references to articles on this complex date back to 1700,[4,5] the earliest available report is that of Peacock,[6] published in 1846. He recognized the special nature of the atrial septal defect and its lack of relation to the foramen ovale, the fact that the atrioventricular orifice is undivided, the deficiency of the interventricular septum, and the cleavage of the aortic cusp of the mitral valve. In his specimen there was an aneurysm of the interventricular septum, a lesion occasionally found in defects associated with ostium primum and which probably represents a smaller degree of deficiency of the interventricular septum than the more usual type described above. Peacock did not describe the tricuspid valve or the anterior and posterior common leaflets, however.

Subsequent authors[7-18] also failed to describe the valves accurately, and so persistent common atrioventricular canal was not clearly distinguished from ostium primum with cleft mitral valve (see below). In fact, it was not until 1931 that Robson[19] first outlined the modern description and interpretation of these structures. He was undoubtedly aided by having inspected the atrioventricular orifice and its valve cusps from the atrial surface. A photograph of this preparation is reproduced in his article. The same had apparently been done by Keith,[12] who did not arrive at the correct interpretation. Little has been added to the description and understanding of this anomaly since the publication of Robson.

In 1875 Rokitansky[20] described 10 cases of a congenital anomaly which differed considerably from persistent common atrioventricular canal. In these cases there was an ostium primum and a cleft in the aortic cusp of the mitral valve, but the tricuspid valve was presumably intact and the atrioventricular orifice divided into right and left sides. There was no ventricular septal opening, although Rokitansky believed that the upper posterior part of the ventricular septum was deficient to a variable extent and that the atrioventricular valves were displaced downward to the crest of the remainder. These were probably the first adequately described cases of what is now known as "ostium primum" or, more accurately, ostium primum with cleft mitral valve. This complex may be regarded as a less complete form of the quadruple complex, since only two of the four features are present. Hence the term partial AV canal has often been applied to describe this combination of lesions, but it seems inaccurate in the strict sense since, there is no persistence of the fetal common atrioventricular orifice in these cases. The relationship of the various valve leaflets may be seen in the middle part of Figure 3 and in Figure 4, where the atria have been removed and the atrioventricular orifices are seen from above. Owing to the absence of the interatrial septum in this region, the specimen gives the impression that the anterior half of the cleft aortic cusp of the mitral valve is continuous with the anterior cusp of the tricuspid valve. In addition, the posterior half of the cleft aortic cusp of the mitral valve appears to be continuous with

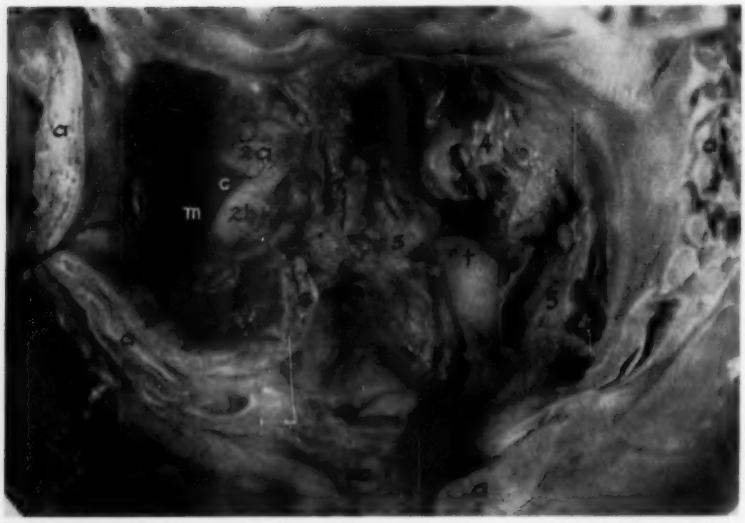

Fig. 4.—Heart of Case 12, with atria removed, seen from above. (*m*) Mitral orifice; (*t*) tricuspid orifice; (*a*) atrial wall; (*s*) interatrial septum; (*c*) cleft in aortic leaflet of mitral valve. Orientation and numbering of valve leaflets is similar to Figure 3.

the septal cusp of tricuspid valve on their atrial surfaces. However, in the presence of an intact septum on the ventricular surface there is no real fusion of the right and left-sided cusps as in AV canal.

Rokitansky did not point out the distinction between these 10 cases and those of the type reported by Peacock. Gellert [21] seems to have been the first to have clearly differentiated between these two types. Abbott [22] placed the two types under entirely separate headings, "persistent ostium atrioventriculare commune" and "defect of the interauricular septum below," thus tending to minimize the resemblance of the two. Rogers and Edwards [3] have questioned the significance of this differentiation. Wakai and Edwards [23] and Campbell and Missen,[24] realizing that there are varying degrees of severity of the same embryological aberration, have proposed nomenclature and schemes of classification which include persistent common atrioventricular canal, ostium primum with cleft mitral valve, and intermediate defects (see Type III ABC, below).

Since AV canal is a complex anomaly with four features and ostium primum with

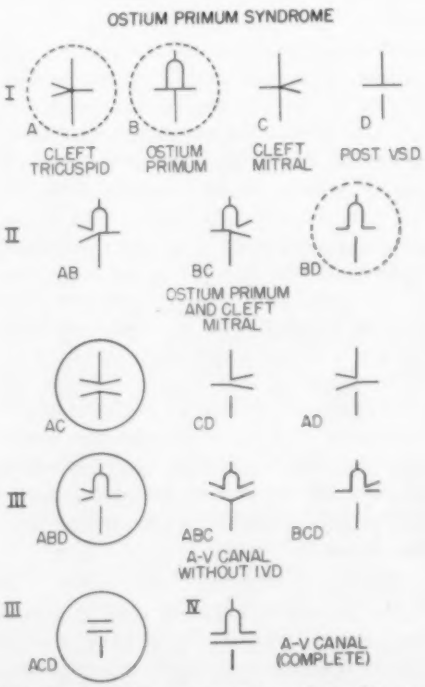

Fig. 5.—Symbolic representation of the 14 possible combinations of the four component lesions of AV canal. Those enclosed in solid circles have not been reported; those in dotted circles probably have, and the others definitely have.

cleft mitral valve has only two of the four, it occurred to us that many other combinations would be possible. Theoretically, there could be four isolated lesions, six different double complexes including ostium primum with cleft mitral valve, and four different triple combinations. These possibilities are summarized symbolically in Figure 5. Those enclosed in solid circles are hypothetical at present, those in dotted circles possibly have been reported, and those not enclosed are definitely known to exist.

Isolated Ostium Primum.—It must be emphasized that isolated ostium primum without abnormality of the atrioventricular valves is rare (Type I B). There are many articles, for example those of Reinhard,[7] Tüngel,[9] and others which may be found in the bibliographies of Gellert [21] and Herxheimer,[25] in which ostium primum is reported without a description of the valves, and so one cannot escape the suspicion that a valvular lesion was overlooked. In one of Rokitansky's cases (Case 1497) the cleft in the mitral valve was shallow, and another without abnormal valves was not actually ostium primum (Case 2184) but a posterior interatrial defect near the orifices of the venae cavae. Maude Abbott * stated that cases of persistent ostium primum "are always associated with cleavage and insufficiency of the anterior mitral segment." Wakai and Edwards [23] have stated that they have never seen an isolated ostium primum. The only reported examples which have come to our attention are one presented at a clinicopathologic conference at the University of Kansas Medical Center [26] and one of Blount's [27] cases (Case 3). In the former case, the diagnosis of Lutembacher's syndrome was made by the discusser, but the mitral valve was reported to be normal at autopsy.

Isolated Cleavage of the Aortic Cusp of the Mitral Valve (Type I C).—This type has been reported by Edwards et al.[28] and Wakai and Edwards,[23] who consider it to be a partial form of common atrioventricular canal.

Isolated Interventricular Defect of the Type Seen in AV Canal (Type I D).—This type may be represented by cases of aneurysm of the interventricular septum under the atrioventricular valves, although only an incomplete degree of patency exists. Such cases have been reported by Rokitansky,† Rogers et al.,[29] and others. Rogers and his co-authors pointed out the relationship to AV canal and cited the cases of Reinhard (Case 3) [7] and Tüngel,[9] where aneurysm of the interventricular septum occurred together with ostium primum. One can also cite Peacock's case,[6] where the interventricular component of an otherwise complete persistent common atrioventricular canal is represented by an aneurysm of the interventricular septum, and Rokitansky's ‡ (Case 2633), where an aneurysm of the interventricular septum coexisted with cleavage of the aortic cusp of the mitral valve. There can be little doubt, therefore, that isolated aneurysm of the interventricular septum is embryologically related to AV canal.

Isolated Cleavage of the Septal Cusp of the Tricuspid Valve (Type I A).—This type has not been reported, but isolated congenital deformity of this leaflet occurred in a case described in Abbott's atlas,§ and one may speculate that the malformation is the result of a mild degree of the same abnormal embryological process that produces cleavage.

Cleft Mitral and Tricuspid Valves Without Any Septal Defect.—Of the six possible double lesions only one, cleft mitral and tricuspid valves without any septal defect (Type II AC), is apparently unreported.

Ostium Primum with Cleft Septal Leaflet of the Tricuspid Valve (Type II AB).—This type was described by Gunn and Dieckman.[18] Blount's [27] Case 2 had ostium

* Reference 22, p. 34.

† Reference 20, Appendix.

‡ Reference 20, Appendix.

§ Reference 22, p. 24.

primum with a shortened septal tricuspid leaflet bound to the ventricular septum.

Ostium Primum with Cleft Mitral Valve (Type II BC).—This type has been described above in detail.

Ostium Primum with Aneurysm of the Interventricular Septum (Type II BD).—Cases of this type have been cited,[7,9] but, because of incomplete description of the valves, one cannot be certain that these were the only two of the four possible features present.

Aneurysm of the Ventricular Septum with Cleft Mitral Valve (Type II CD).—Rokitansky's || case (Case 2633) of this type has already been mentioned also.

Ventricular Septal Defect with Deformity of the Septal Cusp of the Tricuspid Valve.

Among 54 cases of defect at the base of the interventricular septum, Abbott [30] found five with congenital deformity of the septal cusp of the tricuspid valve producing insufficiency (Type II AD). Two such cases have been reported more recently by Stahlman et al.[31] The anomaly of the valve in these instances has been shortening or adhesion to the interventricular septum, but it is possible that this combination corresponds to the sixth double lesion. Its relation to the development of the right tubercles of the endocardial cushions and the conus septum has been pointed out by the latter group of authors.

|| Reference 20, Appendix.

Triple Lesions.—Of the four possible triple lesions, two are known. Ostium primum with cleft mitral and tricuspid valves (Type III ABC) would seem to be represented by those cases of AV canal in which the anterior and posterior common leaflets are so closely attached to the crest of the interventricular septum that no interventricular communication exists. Rogers and Rudolph [32] reported such a case and stated that the membranous interventricular septum was intact, but they did not distinguish it from the usual case of AV canal. Wakai and Edwards [23] and Campbell and Missen [24] have pointed out this difference in three cases and one case, respectively. Whether the ventricular septum is anatomically normal in this type of complex is subject to doubt. Wakai and Edwards [23] also mention a case of ostium primum with cleft mitral valve and interventricular septal defect (Type III BCD).

Embryology

Embryology provides a plausible explanation for AV canal and the related complexes. It is not our purpose to review completely and study the embryological development of these malformations, but the brief summary which follows will aid in understanding the anomalies.[3,33] Early in the fifth week of development the appearance of the interior of the heart is as shown in Figure 6*A*.

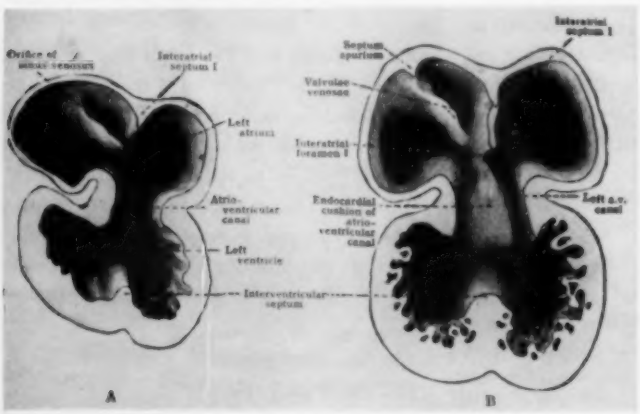

Fig. 6.—Reconstruction of the interior of the mammalian heart (*A*) in the fifth week and (*B*) in the sixth week of gestation. (Reproduced with permission from Patten,[33] The Blakiston Company [division of McGraw-Hill Book Company, Inc.].)

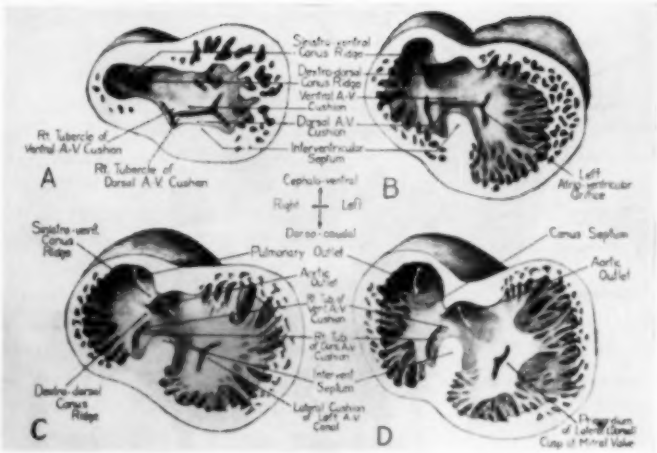

Fig. 7.—Four stages in the partitioning of the atrioventricular canal. (Reproduced with permission from Patten,[28] after Kramer, T. C.: *American Journal of Anatomy* 71:343, 1942.)

There is essentially a single atrium and ventricle, the two being connected by an undivided channel (common atrioventricular canal) formed by a constriction in the wall of the heart tube. About a week later (Fig. 6*B*) division of the atrium and ventricle into right and left sides has begun with development of the interventricular and the primary interatrial septa. The interatrial communication below the septum primum is known as the ostium primum. Division of the atrioventricular canal into right and left sides has also begun by the outgrowth of the dorsal and ventral atrioventricular endocardial cushions from the posterior and anterior walls of the canal. These structures have depth as well as breadth and are destined to complete the division of the heart into right and left sides as well as to divide the atria from the ventricles. The progress of the latter process is seen in Figure 7 from the atrial aspect. As the two endocardial cushions approach one another and fuse, the atria are divided from the ventricles by a structure with appropriate slits dividing it into valve leaflets. During the seventh week the endocardial cushions are completing the right and left division of the atria and ventricles by forming the posterior part of the membranous interventricular septum and by fusing with the inferior margin of the primary interatrial septum. The relations of these structures in the fully formed heart can be seen in Figure 8. The septal cusps of the mitral and tricuspid valves, the posterior part of the membranous interventricular septum, and the central core at the base of the interatrial septum have been contributed by the endocardial cushions. The appearance of the ostium secundum in the septum primum at a location separate from the ostium primum and its closure by the septum secundum occur independently of the events at the atrioventricular region with which we are directly concerned.

Clinical Features and Diagnosis

Until recently pediatricians and internists have had little interest in defects associated with ostium primum as clinical entities. The literature contains scant information on the physical and physiological findings. Observations have been made in case reports, but little comment has been made concerning their diagnostic value, and no one had attempted to discover any clinical features common to several cases until the recent articles by Blount et al.[27] and Brandenburg and DuShane.[34] Nonspecific findings such as intolerance of exercise, failure of growth, recurrent pneumonia, intermittent cyanosis, dyspnea, cardiomegaly, congestive failure, and pulmonary hypertension, although they are often mentioned, are of little diagnostic

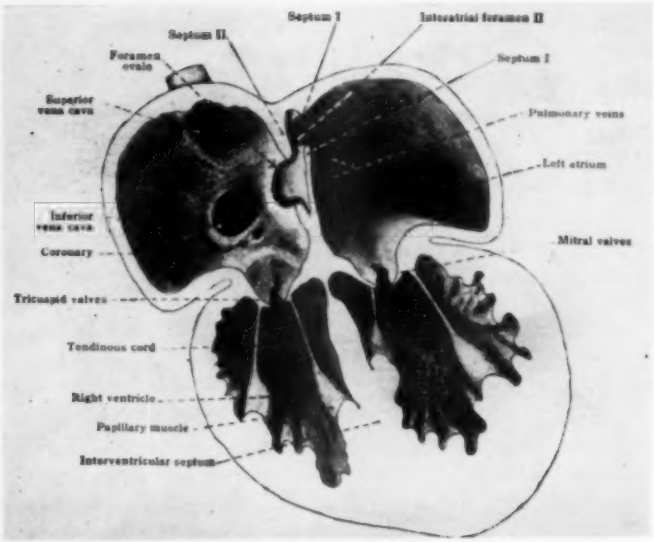

Fig. 8.—Longitudinal section of the heart in the latter part of fetal life. (Reproduced with permission from Patten,[42] The Blakiston Company [division of McGraw-Hill Book Company, Inc.].)

importance, since they are common to many types of lesions with left-to-right shunts and do not help to distinguish those associated with ostium primum from others.

Our purpose in undertaking the present study was to discover what features of the clinical examination and physiologic and radiological data in defects associated with ostium primum might be sufficiently distinctive to differentiate them from other types of septal defect.

A correlation with Mongolism has been noted and has become familiar through the works of Abbott[22] and Taussig.[35] Taussig states that AV canal is to be expected in patients with Mongolism and acyanotic congenital cardiac defects superficially resembling interventricular septal defect. Rogers and Edwards[3] have shown that this relationship has been overemphasized, since only a minority of persons affected by Mongolism and congenital heart disease have a defect associated with ostium primum. The same conclusion was reached by Kaiser and Schmid.[36] Conversely, Rogers and Edwards[3] reviewed 55 cases of AV canal and ostium primum with cleft mitral valve, among which there were 8 cases without Mongolism, 17 with Mongolism, and 30 in whom the information had not been given by the original authors. We find that of the 17 with Mongolism 2 had ostium primum with cleft mitral valve and 12 had AV canal, while there were insufficient data to distinguish which was present in 3. Even the minimum of 17 of 55 gives a high incidence of Mongolism among patients with defects associated with ostium primum.

The presence of a thrill was noted by Moore[37] in 1881 and in occasional reports[13,26,27,38,39] since his time but has not been considered to be particularly noteworthy, although it is listed by Metianu et al.[40] and Watkins and Gross[41] as one of the characteristics of AV canal. Suprisingly, one was present in the case of ostium primum with allegedly normal mitral valve mentioned,[26] although there was none in Case 3 of Blount et al.[27] The latter authors reported a thrill in only one of their five cases of various types of defect associated with ostium primum. Systolic murmurs have been mentioned frequently. An apical location has been recorded in both AV canal and ostium primum with cleft mitral valve by numerous authors,[3,9,10,19,27,32,42-46] beginning with Tüngel[9] in 1864. No one seemed

to consider the fact remarkable until Cahen et al.[38] (1952) reported two autopsied cases of ostium primum with cleft mitral valve which had been misdiagnosed during life as Lutembacher's syndrome because of evidence of interatrial defect with systolic and diastolic murmurs having a mitral distribution. In a footnote to an article on atrial septal defects, Braudo et al.[47] mentioned two cases characterized by location of the systolic murmur between the left sternal border and apex in which holes low in the septum with congenital mitral insufficiency were found. An apical systolic murmur was found in two of Blount's five cases[27] and is now a fairly well recognized sign in defects associated with ostium primum.[24,34,48-50] Diastolic murmurs have been noted as well, but the location and timing vary from case to case, although often they are mistaken for the murmur of mitral stenosis.[3,19,26,27,37-39,42] Occasionally no murmur has been found in AV canal[3,50,51] or incompletely described defects with ostium primum.[8]

There are at least 24 cases in the literature with prolongation of the P-R interval on the electrocardiogram.[24,26,27,38,39,46,52,53] Cahen et al.[38] also made note of the ease with which complete atrioventricular block ensues in such patients. Metianu et al.[40] have recognized that prolongation of the P-R interval has diagnostic significance in cases of AV canal. The combination of left axis deviation and hypertrophy of the right or possibly both ventricles, which is now familiar as a sign of AV canal or ostium primum with cleft mitral valve, has been referred to by Manning and Taussig[49] and Harned et al.[34] and has been reported in three of five cases by Blount et al.[27] A qRs pattern in Lead aV_L has also been observed frequently. All of these findings have been discussed and illustrated by Toscano-Barbosa et al.[53]

So far as x-ray findings are concerned, almost all of the interpretations in published case reports have dealt with generalized enlargement, right ventricular enlargement, pulmonary artery enlargement, and increased pulmonary vascular markings, none of which is helpful in distinguishing defects associated with ostium primum from other types of septal defect. Little attention has been directed to the left atrium and ventricle except in the case of Rogers and Rudolph,[32] where left ventricular enlargement was more marked than right ventricular enlargement; in Case 10 of Rudolph et al.,[39] that proved to be AV canal at autopsy, in which left atrial enlargement was reported and left ventricular enlargement is apparent in the illustration; in four of Blount's cases in which there was left ventricular enlargement, and in Case 1 of Campbell and Missen.[24] Manning and Taussig[49] found enlargement of all four chambers in cases of ostium primum with cleft mitral valve. Others[40,50] have not found enlargement of the left-sided chambers, although in Figure 358a of Kjellberg et al.[50] marked left ventricular enlargement would be present by our criteria. The latter authors have also reported the only published angiocardiographic data in a defect associated with ostium primum. A defective interventricular septum was visualized by selective angiocardiography, the contrast medium being injected first into the right and then into the left ventricle, because of displacement of the catheter during the injection. Regurgitation into both atria was also observed, and autopsy showed that the patient had AV canal.

Catheterization data have been published infrequently in defects associated with ostium primum. In the case from the University of Kansas,[26] in which there was apparently an isolated ostium primum, a left-to-right shunt was found at the atrial level only, as might be expected, and the same was true in Blount's series of five cases, in all of which the interventricular septum was thought to be intact. However, Rudolph et al.[39] also observed interatrial shunt alone in a case later proved to have AV canal. Wakai et al.[55] found interatrial shunt alone in three cases and shunts at both the atrial

and ventricular levels in eight. Pulmonary hypertension has been thought to be associated with ostium primum more frequently than with ostium secundum.[26,27,40,50] Taussig[35] believed that arterial desaturation was usually present in cases of AV canal, but in published case reports the arterial blood has usually been fully saturated.[39,55,56] Some authors state that the catheter readily enters the left side of the heart in defects associated with ostium primum and may pass from the right atrium to the left ventricle in such a way to be diagnostic.[40,55-57]

Material and Methods

Twelve patients in whom the lesion was diagnosed at autopsy and two who are alive postoperatively, in whom it was observed at operation, have been collected from admissions to the University of Minnesota Hospitals and Kings County Hospital, Brooklyn. In nine patients (Cases 1, 2, 6, and 9-14) the heart specimen was examined by us. Of the 12 who were autopsied, 6 (Cases 2, 3, 5, 9, 10, and 14) had persistent common atrioventricular canal and 5 (Cases 1, 6, and 11-13) had ostium primum with cleft mitral valve. The other autopsied case (Case 4) and the two who survived operation (Cases 7 and 8) had a persistent ostium primum, but little else is known about the exact nature of the anomaly. In none of these 14 patients was there evidence of complicating defects other than those which form part of the complex of AV canal or ostium primum with cleft mitral valve. Ages ranged from 4½ months to 48 years, 12 being in the pediatric and 2 in the adult age group. All had heart catheterizations.

For comparison, 20 patients with ventricular septal defect, 8 patients with separate atrial and ventricular septal defects, 25 patients with atrial septal defect other than ostium primum, and 4 patients with Lutembacher's syndrome were studied. Most of these control cases were surgical patients. These groups were examined by the same methods used for the group with ostium primum.

Two of the patients with defects associated with ostium primum (Cases 1 and 9) are presented below, while the entire series is summarized in Table 1. The control patients are summarized in Table 2.

Report of Cases

Case 1.—A girl was first referred to the cardiac clinic of the University of Minnesota Hospitals in June, 1947, at the age of 2 years. Her birth weight was 3900 gm. From infancy she had been noted to have a precordial bulge and pulsations in the neck. At the end of the second year she was taken to the family doctor because of exertional dyspnea, orthopnea, intermittent cyanosis, and anorexia. A murmur was discovered at that time.

On physical examination she was a small girl, weighing 10 kg., having normal vital signs, and without manifestation of Mongolism. She was pale but acyanotic. Orthopnea, a precordial bulge, and cardiomegaly were noted. There was a thrill in the third and fourth left intercostal spaces and a loud blowing systolic murmur, which was equally well heard at the left sternal border, apex, and left axilla and also well heard over the back. There was a diastolic murmur at the apex and left sternal border as well. The pulmonic second sound was accentuated. The liver was not enlarged at that time; there were good femoral pulses, and she had no clubbing or edema.

Electrocardiograms showed peaked, notched, broad P-waves, a prolonged P-R interval (0.20 second at a rate of 105 per minute), a QRS axis of −75 degrees, qRS pattern in Lead aV_L with rSr's' pattern in Lead aV_R, and right ventricular hypertrophy in the precordial leads. Incomplete right bundle branch block (rsR' pattern) was not definitely present in Lead V_1. Fluoroscopy and films of the heart showed marked cardiomegaly due to great enlargement of the right ventricle and slight enlargement of the left ventricle. There was slight left atrial enlargement, and the pulmonary artery and peripheral lung vascular markings were prominent. The aorta was hypoplastic.

She was followed with the presumptive diagnosis of Lutembacher's syndrome and continued to do poorly, having spells consisting of tachycardia, increased orthopnea, and cyanosis of the nailbeds. At the age of 5 she was admitted because of frank congestive failure and lobar pneumonia, which responded to digitalis and antibiotics. Shortly thereafter cardiac catheterization was performed. It showed an increase of 6.0 vol. % in oxygen content in the right atrium without further arterialization in the ventricle. The pressures were 10/2 mm. Hg in the right atrium and 40/0 in the right ventricle, but the pulmonary artery was not entered, and an arterial sample was not obtained.

At the age of 5½ an exploratory operation revealed the absence of mitral stenosis. Five months later a second operation was done in an attempt to close the defect, with use of a pump oxygenator, but cardiac arrest occurred, and the patient died.

At autopsy the heart appeared enlarged, and the pulmonary artery was large in comparison to the aorta. There was a persistent ostium primum, but the atrioventricular orifice was divided into right and left sides. The posterior leaflet of the mitral valve was normal, but the aortic cusp was deeply cleft to its attachment to the interventricular sep-

TABLE 1.—*Summary of Our Fourteen Cases with Persistent Ostium Primum**

		Pathology									Physical Examination						Electrocardiogram					
											Systolic Murmur											
Case	Age, Yr.	Ostium Primum	Common AV Orifice	Cleft Mitral Cusp	Cleft Tricuspid Cusp	IVSD	Operation	Autopsy	Mongolism	Thrill	Grade	Location	Diastolic Murmur	P-R Interval	Rate	QRS Axis, Degrees	Electrical Position	Ventricular Hypertrophy	rsR′ in V$_1$
1	6	+	0	+	0	0	+	+	0	+	4	LSB, apex ,axilla, back	+	0.20	105	−75	Horiz.	R	0
2	7/12	+	+	+	+	+	0	+	0	+	4	LSB, apex, axilla	+	0.14	160	−120	—	R	0
3	7/12	+	+	+	+	+	+	+	0	—	3	Base, LSB	0	0.14	156	+120	Horiz.	R	0
4	48	+	—	—	—	—	+	+	0	—	—	Base, apex	0	a. f.	120	−40	Horiz.	R	+
5	4	+	+	+	+	+	+	+	0	+	4	LSB, apex, axilla, back	+	0.10	130	−105	Horiz.	R	0
6	4/12	+	0	+	0	?	+	+	0	+	4	LSB, apex	0	0.12	140	−75	Horiz.	R	0
7	1 4/12	+	—	—	—	—	+	0	0	+	3	LSB, apex	+	0.14	140	+30	Horiz.	R	+
8	7	+	—	—	—	—	+	0	0	+	3	Base, neck, axilla	+	0.24	90	−60	Horiz.	R	0
9	5	+	+	+	+	+	+	+	0	+	3	LSB, apex, back	?	0.16	110	−70	Horiz.	Comp. RBBB	0
10	2 6/12	+	+	+	+	+	+	+	0	+	2	LSB	0	Long	172	?	?	Comp. RBBB	0
11	21	+	0	+	0	0	+	+	0	+	3	Apex, axilla, back	+	0.22	80	−50	Horiz.	R	+
12	4 6/12	+	0	+	0	0	+	+	0	+	3	Apex, axilla, back	+	0.16	120	−30	Horiz.	R+?L	+
13	2	+	0	+	0	0	+	+	0	+	4	LSB, apex	0	0.15	115	−45	Horiz.	R+?L	+
14	4	+	+	+	+	+	+	+	0	+	4	LSB, apex	+	0.20	110	−60	Horiz.	R+?L	+

TABLE 1.—*Summary of Our Fourteen Cases with Persistent Ostium Primum**—Continued

	X-Ray							Catheterization Data							Remarks
Case	Generalized Enlargement	RV Enlargement	LV Enlargement	LA Enlargement	Pulmonary Artery Enlargement	Pulmonary Vascular Markings	Small Aorta	Route	RA Pressure, Mm. Hg.	RV Pressure, Mm. Hg.	PA Pressure, Mm. Hg.	IA Shunt, Vol. % †	IV Shunt, Vol. % ‡	Other Chambers Entered	Arterial O_2 Saturation, %	
1	3+	3+	1+	1+	3+	3+	+	IVC	10/2	40/0	—	6.0	0	0	—	Diagnosed as Lutembacher's syndrome
2	4+	3+	2+	1+	2+	3+	—	IVC	—	90/0	—	4.1	0.6	0	62	In extremis; Lead aV_L not taken
3	3+	3+	2+	0	2+	3+	—	IVC	—	—	—	1.6	—	—	—	Condition poor
4	3+	3+	1+	2+	3+	2+	+	SVC	24/6 (M 10)	38/9	47/13	4.9	1.8	0	96	
5	3+	3+	2+	2+	4+	3+	+	IVC	0/—5	30/0	28/14	6.2	0	LA	—	
6	3+	2+	1+	2+	2+	2+	—	IVC	4/2	35/3	—	0	2.7	0	95	
7	3+	3+	2+	2+	2+	3+	—	—	M 3	55/0	55/30	38%§	27%§	0	95	
8	3+	3+	2+	1+	2+	2+	0	SVC	7/0	33/4	24/8	3.2	0	LA LV	100	Diagnosed as Lutembacher's syndrome
9	4+	3+	2+	2+	2+	2+	—	—	M 7.1	108/12	85-106 /45	5.2	0	0	94	Taking digitalis
10	3+	3+	2+	2+	3+	2+	+	IVC	8/0	49/0	—	2.5	0.6	LA LV	96	
11	3+	3+	0	0	2+	2+	+	SVC	3.5/0 (M 2)	25/3	23/7 (M 11)	3.3	0.03	0	94	
12	2+	3+	2+	2+	2+	2+	+	SVC	—	—	—	1.3	0.9	0	93	Catheterization 12/53;
								SVC	—	60/0	49/23	1.5	0	0	93	Catheterization 11/54
13	3+	3+	—	3+	2+	2+	+	IVC	8/0	41/0	32/18	2.0	1.1	0	92	
14	3+	3+	?	1+	3+	3+	—	IVC	15/5	60/0	—	2.4	1.3	0	87	

* +, Positive; 0, negative; —, data not obtained or does not apply; Comp., complete; LSB, left sternal border; M, mean pressure; a.f., auricular fibrillation.
† Difference in O_2 content between venae cavae and right atrium.
‡ Difference in O_2 content between right atrium and right ventricle.
§ Difference in oximeter readings.

TABLE 2.—*Control Cases**

Case IV defects	Age, Yr.	Autopsy	Operation	Thrill	Apical Systolic Murmur	Diastolic Murmur	Prolonged P-R	Horizontal Heart	LAD & RVH	IA Shunt	IV Shunt	PA (or RV) Systolic Pressure, mm. Hg	Left Atrial Enlargement	Left Ventricular Enlargement	Remarks
1	11/12	+	+	+	+	0	0	0	0	0	+	46	?	+	
2	4	0	+	+	?	0	0	0	0	0	+	30	+	+	
3	5	0	+	+	0	0	0	+	0	0	+	60	0	+	
4	9/12	0	+	+	0	0	0	0	0	0	+	60	+	+	
5	11/12	+	+	?	0	0	?	0	0	—	—	55	+	+	Taking digitalis
6	6/12	0	+	+	0	0	+	0	0	0	+	87	+	+	Taking digitalis
7	1	0	+	+	0	0	+	0	0	0	+	42	+	+	Taking digitalis
8	5	0	+	+	0	0	?	+	0	0	+	80	?	+	Taking digitalis
9	6/12	0	+	+	0	0	0	0	0	0	+	60	+	+	
10	10/12	+	+	+	0	0	0	0	0	0	+	44	+	+	
11	8/12	+	+	0	0	0	0	0	0	0	+	80	+	+	
12	2	0	+	+	0	0	0	0	0	0	0	68rv	+	+	
13	3	0	+	+	?	0	0	+	?	0	+	43	+	+	
14	1	0	+	+	0	0	?	0	0	0	+	55	—	—	Taking digitalis
15	4/12	+	+	+	0	0	0	0	0	0	+	60	+	+	
16	2	0	+	+	0	0	0	0	0	0	+	70	+	+	
17	1	0	+	+	0	0	0	0	0	0	+	60	+	+	
18	6/12	0	+	0	0	0	0	0	0	0	+	46	+	+	
19	6	0	+	+	0	0	+	0	0	0	+	90	+	+	
20	9	0	+	0	0	0	0	?	?	0	+	60	+	+	
Separate IA & IV defects															
1	2	+	+	?	?	0	+	—	—	+	0	50	?	?	No unipolar leads
2	5/12	+	+	—	0	0	0	0	0	+	—	—	+	+	RV not entered
3	10/12	+	0	—	0	0	0	0	0	—	—	—	+	+	Mongolism
4	5/12	+	0	—	0	0	0	0	0	—	—	—	?	0	
5	1	+	+	+	0	0	0	0	0	+	+	85rv	+	0	
6	4	+	+	+	+	0	?	+	?	0	+	103	+	+	Taking digitalis
7	7/12	0	+	+	+	0	0	0	0	+	0	80	0	0	
8	14	+	+	+	+	+	+	?	0	+	0	92rv	+	0	Aorta anterior to PA
IA defect (not ostium primum)															
1	37	+	+	0	0	0	0	+	+	+	—	20	0	0	
2	5	+	+	0	0	0	0	0	0	+	0	30rv	0	0	
3	5	+	+	0	0	0	0	0	0	+	0	19	0	0	Relative pulmonary stenosis
4	3	0	+	0	0	0	0	0	0	+	0	12	0	0	
5	17	0	+	0	0	0	0	0	0	+	0	17	0	0	? Anomalous pulmonary veins; relative pulmonary stenosis
6	10	0	+	0	0	0	0	0	0	+	0	48	0	0	
7	21	0	+	0	0	0	+	0	0	+	0	19	0	0	Relative pulmonary stenosis
8	9	0	+	+	+	+	+	0	0	+	0	34	0	+	Right BBB
9	35	0	+	—	0	0	0	0	0	+	0	32	0	0	
10	35	0	+	0	+	0	0	0	0	+	0	36	0	+	
11	52	0	+	—	0	0	+	0	0	+	0	41	0	0	Anomalous pulmonary veins; taking digitalis
12	18	0	+	0	0	0	0	0	0	+	0	23	0	0	
13	29	0	+	—	0	+	+	+	0	+	0	26	0	+	Taking digitalis
14	8	0	+	0	0	0	0	0	0	+	0	8	0	0	Anomalous pulmonary veins
15	6	0	+	0	0	0	0	0	0	+	0	32	0	0	
16	12	0	+	0	0	+	0	0	0	+	0	14	0	0	
17	25	0	+	0	0	0	0	0	0	+	0	20	0	0	Shunt in pulmonary artery also

TABLE 2.—*Control Cases**—Continued

Case	Age, Yr.	Autopsy	Operation	Thrill	Apical Systolic Murmur	Diastolic Murmur	Prolonged P-R	Horizontal Heart	LAD & RVH	IA Shunt	IV Shunt	PA (or RV) Systolic Pressure, mm. Hg	Left Atrial Enlargement	Left Ventricular Enlargement	Remarks
18	24	0	+	?	0	+	0	0	0	+	0	Normal	0	0	
19	37	0	+	—	—	—	0	0	0	+	0	20	0	0	
20	26	0	+	—	0	0	0	0	0	+	0	31rv	0	+	
21	6	0	+	?	0	0	0	0	0	+	0	20	+	+	Anomalous pulmonary veins
22	12	0	+	0	0	0	?	0	0	+	0	10	0	0	
23	26	0	+	0	0	0	+	0	0	+	0	36rv	0	0	Right BBB
24	14	0	+	0	0	0	0	0	0	+	0	26	0	0	Anomalous pulmonary veins
25	23	0	+	0	0	+	0	0	0	+	0	72	0	0	Diastolic thrill
Lutembacher's syndrome															
1	20	0	+	+	+	+	0	0	0	+	0	39	0	+	
2	26	0	+	—	+	+	af	0	0	+	0	53	+	+	
3	31	0	+	+	+	+	afl	bbb	bbb	+	0	82	0	+	
4	42	0	+	+	0	+	0	0	0	+	0	43	+	+	

*+, positive; 0, negative; —, information not obtained; ?, doubtful or indeterminate; rv, right ventricle; af, auricular fibrillation afl, auricular flutter; bbb, bundle branch block.

tum and thus divided into anterior and posterior halves. The leaflets of the tricuspid valve were relatively normal, but the septal cusp did not extend to the anterior end of the interventricular septum, and so a small gap remained between its anterior edge and the adjacent edge of the anterior leaflet. On the atrial surface the posterior half of the aortic cusp of the mitral valve appeared to be continuous with the posterior cusp of the tricuspid valve (cf. Fig. 4). The interventricular septum did not seem to be defective, its crest extending up to the usual plane of the atrioventricular valves. The valve leaflets were solidly fused to it, and a probe could not be passed between the valves and the interventricular septum, and so no interventricular communication existed. There were no other defects of the heart or great vessels.

This is an example of ostium primum with cleft mitral valve.

CASE 9.—A 5-year-old boy was referred to the University of Minnesota Hospitals for closure of an interatrial septal defect and was admitted in September, 1954. He had been cyanotic for the first 4 days of life, and in infancy he had slight intermittent cyanosis and a poor appetite. He had been hospitalized three times for pneumonia, and increasing exercise-intolerance had been noted during the year prior to admission. Five months prior to admission, heart failure had been diagnosed and digitalis therapy started. The physical examination showed a well-developed and well-nourished acyanotic boy who had no Mongolism. He weighed 19.1 kg. The lungs were clear. He had a marked precordial bulge on the left, and the heart was enlarged to percussion. A soft systolic thrill was felt in the third and fourth intercostal spaces. A loud systolic murmur was heard in the third and fourth interspaces, close to the sternum and at the apex; it was also well heard in the back. The pulmonic second sound was accentuated. He had normal sinus rhythm. Some observers believed that there was also a diastolic murmur. Other than hepatomegaly and splenomegaly, the rest of the examination was normal.

There were peaked, notched P-waves and a prolonged P-R interval (0.16 second at a rate of 110 per minute) on the electrocardiogram. He was taking digitalis at the time the tracing was made. The QRS duration was 0.10 second, and there was evidence of complete right bundle branch block, but without rsR′ pattern in Lead V_1. There was a strong R_I, S_{II}, S_{III} pattern, so that the electrical axis was −70 degrees in spite of the right bundle branch block, and a qRs pattern was present in Lead aV_L with RS in Lead aV_F. Heart fluoroscopy and films showed a severely enlarged heart with much right ventricular and considerable left ventricular enlargement. There was enlargement of the pulmonary artery segment, the root shadows, and the peripheral pulmonary vessels. The left atrium was moderately enlarged. Catheterization, which had been done at the University of Alberta Hospital, showed a 5.2 vol. % increase in oxygen content at the atrial level but none in the ventricle or pulmonary artery. The femoral artery sample was 94% saturated. The right atrial mean pressure was 7.1 mm. Hg, and the right ventricular pres-

sure was 108/12 mm. Hg; that in the pulmonary artery was 85 to 106/45 mm. Hg.

The possibility that this was an ostium primum defect of some kind was considered preoperatively because of the enlargement of the left atrium, the pulmonary hypertension, the history of cyanosis, and the severity of the symptoms. The operation was performed under hypothermia, but persistent common atrioventricular canal was found, and the defect could not be closed without disturbing the atrioventricular valves. The patient did not survive.

At autopsy the interatrial septum had two defects, an ostium secundum and an ostium primum. The atrioventricular orifice was undivided and had five valve leaflets—two long anterior and posterior leaflets crossing the interventricular septum and common to both ventricles, one normal posterior mitral leaflet, and normal posterior and anterior tricuspid leaflets. The interventricular septum had a depression in its superior margin under the atrioventricular orifices, and the anterior and posterior leaflets were attached to its free margin by chordae tendineae. The tip of a hemostat could be passed between both leaflets and the underlying crest of the interventricular septum among the chordae tendineae, and so interventricular communication was present. The right atrium, the right ventricle, and also the left ventricle were enlarged, and the aorta was small. There was no other cardiovascular anomaly.

This is an example of persistent common atrioventricular canal.

Differential Diagnosis of Ostium Primum

The 14 cases presented here illustrate, in a series larger than any heretofore published in detail, 10 distinctive features by which defects associated with ostium primum may be differentiated from other septal defects.

1. *Thrill.*—A systolic thrill was present in all 12 of the patients with ostium primum in which any observation was made on this point. In a few instances its location was noted to be apical, and once it was felt on the back. It is undoubtedly due to regurgitation from the atrioventricular valves. It was found in only 1 of 20 cases of atrial septal defect other than ostium primum where the data were available; therefore, it is very useful in distinguishing ostium primum from other types of atrial defect when catheterization shows a left-to-right shunt at the atrial level. As would be expected, a thrill was found frequently in the cases of ventricular septal defect and Lutembacher's syndrome. It was also definitely present in 50% of those with separate interatrial and interventricular defects.

2. *Apical Systolic Murmur.*—A systolic murmur with location similar to that heard in rheumatic mitral insufficiency, that is, maximal at the apex, was heard in 12 of the 14 patients with ostium primum. There may be transmission to the left axilla, or the murmur may be equally loud at the apex and lower left sternal border. A murmur of this type occurred definitely in only 2 of 24 cases of atrial septal defect other than ostium primum and in only 1 of 20 cases of ventricular septal defect. It was common in Lutembacher's syndrome and was found in three of the eight patients with separate atrial and ventricular defects. The natural assumption that this murmur is caused by the cleft in the mitral valve is confirmed by the fact that it was still present in Cases 8 and 11 after closure of the ostium primum alone.

3. *Diastolic Murmur.*—Diastolic murmurs were present in 8 or 9 of the 14 patients with ostium primum. Sometimes the location was apical, as in Cases 1, 2, and 8, making the similarity to rheumatic mitral involvement very close, but oftener the chart failed to indicate the exact location, and apparently it is highly variable from patient to patient. We have therefore merely noted the frequent presence of a diastolic murmur without trying to characterize it further. In atrial septal defects other than ostium primum, a diastolic murmur was heard in 5 of 24 cases where the information was available. There were 9 in 20 patients with interventricular septal defect and only 1 in the 8 with separate atrial and ventricular defects. On the other hand, all four of the patients operated on with Lutembacher's syndrome had diastolic murmurs.

4. *Prolongation of the P-R Interval.*—This sign was definitely found in 11 of the 13 patients with ostium primum in whom the fact could be determined. In Case 5 it was borderline, and in Case 6, normal; Case 4 had auricular fibrillation. Only 1 of the 11 (Case 9) was taking digitalis when the tracing showing a prolonged P-R interval was made. The same was definitely present in the absence of digitalis in only 3 of 23 patients with atrial septal defect other than ostium primum, in only 1 of 15 with ventricular septal defect, in 2 of the 8 with separate interatrial and interventricular defects, and in none of those with Lutembacher's syndrome. None of our patients with ostium primum had complete atrioventricular block spontaneously, but in Cases 4, 8, 11, and 12 it occurred after operation.

5. *Left Axis Deviation Pattern and Right Ventricular Preponderance.*—The combination of left axis deviation pattern and right ventricular preponderance was present in 10 cases. Two had complete right bundle branch block, and so ventricular preponderance could not be assessed, but one of them (Case 9) had an electrical axis of −70 degrees. One patient had a normal axis, and one patient had right axis deviation. Left axis deviation and right ventricular hypertrophy did not occur in any of the 20 patients with interventricular defect, the 8 with combined septal defects, or the 4 with Lutembacher's syndrome, although it was observed in 1 of the 25 with interatrial defects other than ostium primum.

6. *"Horizontal Heart."*—A qRs pattern in Lead aV_L with rS or RS in Lead aV_F ("horizontal heart") is also characteristic of defects associated with ostium primum, having occurred in 12 of the 13 patients for whom the data were available in this series. This configuration usually reflected left axis deviation in the standard leads, but in Case 3 it was present in spite of right axis deviation and in Case 7 it occurred with normal axis. It may therefore be useful occasionally in arousing the suspicion of ostium primum when the standard leads are atypical.

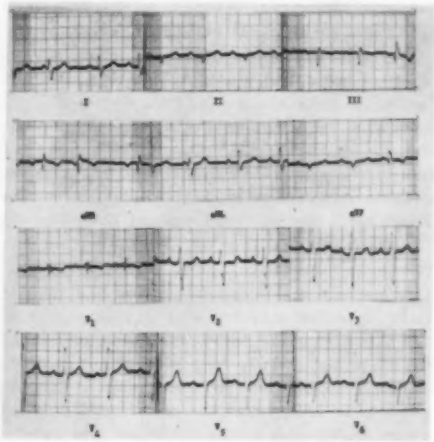

Fig. 9.—Electrocardiogram in Case 11. P-R interval 0.22 second. Ventricular premature beats. Mean QRS axis, −50 degrees. Horizontal heart. Probably incomplete right bundle branch block. Right ventricular hypertrophy.

"Horizontal heart" was found in 2 of 25 patients with interatrial defect other than ostium primum, 3 of 20 with ventricular septal defect, 1 of 7 with separate atrial and ventricular defects, and none of 3 with Lutembacher's syndrome, the information being unavailable in the remainder.

Most of the electrocardiographic features of ostium primum may be seen in Figure 9.

7. *Left Ventricular Enlargement.*—Radiologic examination showed left ventricular enlargement in 10 of our 12 patients for whom the films were satisfactory. Although common in ventricular septal defect (19 of 19 cases) and Lutembacher's syndrome (4 of 4 cases) and not rare in combined interatrial and interventricular defects (3 of 8 cases), it was unusual (5 of 25 cases) in interatrial septal defects other than ostium primum.

8. *Left Atrial Enlargement.*—This sign was present in 12 of the 14 patients with ostium primum, 16 of 19 with interventricular defect, 2 of the 4 with Lutembacher's syndrome, 5 of the 8 with separate interatrial and interventricular septal defects, and only 1 of the 25 with atrial defects other

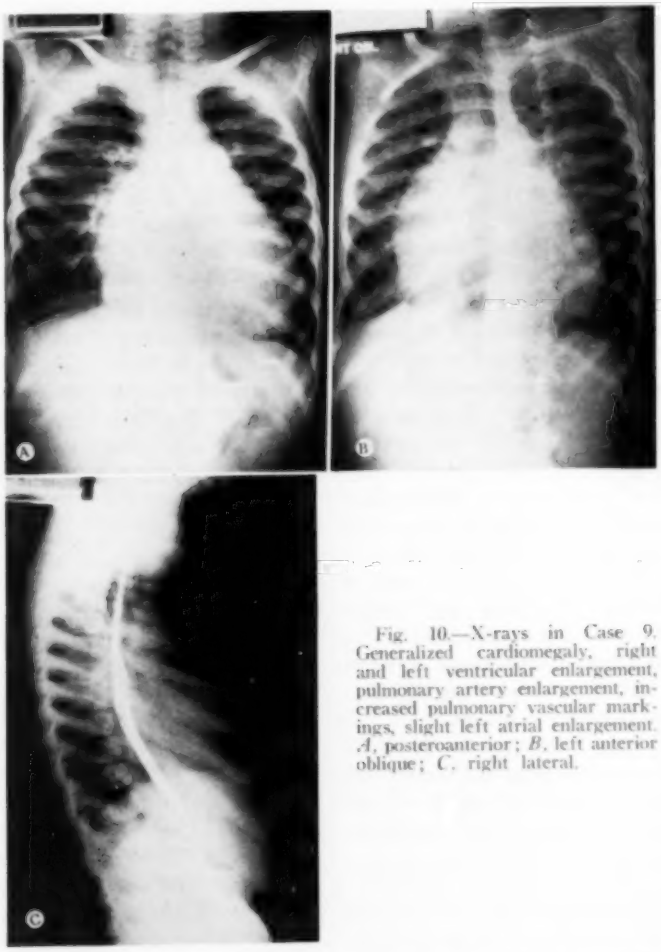

Fig. 10.—X-rays in Case 9. Generalized cardiomegaly, right and left ventricular enlargement, pulmonary artery enlargement, increased pulmonary vascular markings, slight left atrial enlargement. *A*, posteroanterior; *B*, left anterior oblique; *C*, right lateral.

than ostium primum. The degree of left atrial enlargement in ostium primum syndrome is somewhat less than that seen in interventricular septal defect and patent ductus when the age group and clinical severity are roughly similar. Figure 10 shows radiographs from a typical case (Case 9). Angiocardiography was done in only one case (Case 3) and was not helpful in making the diagnosis.

9. *Interatrial Left-to-Right Shunt.*—Interatrial left-to-right shunt without interventricular left-to-right shunt was the commonest finding at catheterization in our series, regardless of the type of lesion. A significant amount of arterialization of the right atrial blood without significant further arterialization of the ventricular blood was found in seven patients. Only four had both interatrial and interventricular shunts (Cases 4, 7, 13, and 14). In Case 3 an interatrial shunt was not strictly present according to the criteria, and the ventricle was not entered. In Case 6 the data apparently showed an interventricular left-to-right shunt only. Case 12 was catheterized twice, but no unequivocal shunt was demonstrated at the atrial level, although an interventricular shunt was probably present on the first occasion. In Case 13 two shunts appeared

to be present, although there was no interventricular defect at autopsy. Interatrial shunt alone also occurred in three of five cases with separate interatrial and interventricular defects in which complete catheterization data were obtained.

10. *Pulmonary Hypertension.*—Pulmonary hypertension (right ventricular or pulmonary artery pressure greater than 30 mm. Hg) was present in 9 of the 13 patients with ostium primum in which pressures were obtained, and no significant degree of "relative pulmonary stenosis" (right ventricular pressure greater than pulmonary artery pressure) was observed in 8 patients where both of these structures were entered. Pulmonary hypertension was present in 7 of the 22 cases of interatrial defect other than ostium primum in which the pulmonary artery pressure was obtained and was very common in the other groups of control patients (Table 2). In three cases (Cases 1, 4, and 14) the right atrial pressure was elevated. In Case 4 there was a giant c-wave, indicating tricuspid insufficiency. Arterial desaturation was found to be uncommon, occurring in only 2 of the 11 of our cases (2 and 14) who had this determination; Case 2, who had AV canal, was extremely ill at the time of catheterization. The left ventricle was entered in only two of our series, of which one was proved to have AV canal at autopsy, and the other has had operation only, but in each instance the catheter entered the left atrium first and did not pass directly from the right atrium to the left ventricle.

Comment

It is our impression that the variations in the pathological picture in these entities have often been inadequately described. The two following suggestions may help to clarify this problem. One is that there should be more general familiarity with the possible combinations of lesions associated with ostium primum. The other is that one should follow the practice of removing the atria and inspecting the atrioventricular orifices from the atrial surface whenever ostium primum was suspected ante mortem or is discovered when the atrium is opened. A dissection of this kind is shown in Figure 4.

It is important for practical as well as theoretical reasons to gain a useful concept of the relationship of these lesions to one another. Contrary to the opinion of some authors, we prefer to consider them as individual members of a family of conditions which are closely related embryologically and clinically. Certainly it will be necessary for the surgeon to know whether he must deal with ostium primum, cleft mitral valve, cleft tricuspid valve, and interventricular septal defect or only with ostium primum and cleft mitral valve or with some other combination.

The embryological relationship is based on the fact that all these defects result from defective development of the endocardial cushions. Since these structures extend both longitudinally and transversely through the atrioventricular region of the developing heart, it is helpful to think of each cushion as having a superior and an inferior portion as well as left and right tubercles. It is obvious from Figures 7 and 8 that if there were complete failure of fusion of the dorsal and ventral endocardial cushions the defect called persistent common atrioventricular canal would result. The similarity of the structures in Figure 7 to the valve arrangement in AV canal (cf. Fig. 3) is striking. Ostium primum with cleft mitral valve probably respresents the result of failure of fusion of only the left tubercles of the endocardial cushions. By this reasoning, an isolated ostium primum defect would be the result of failure of union of the superior portion only of the left tubercles, and isolated cleavage of the mitral valve would be the result of failure of fusion of the inferior portions. This type of ventricular defect would be related to failure of fusion of the inferior portion of the right tubercles, and cleft tricuspid valve, to failure of fusion of the superior portion of the right tubercles.

The various other double and triple combinations would be caused by failure of union of the two or three appropriate parts of the endocardial cushions. Perhaps the rarity of ostium primum without valvular defects may be accounted for by the fact that this opening results from failure of the septum primum to be fused to the superior segment of the left endocardial tubercle rather than from deficient development of the septum itself. Therefore, it usually occurs in association with other endocardial cushion anomalies. This rarity is of great significance. First, the presence of cleavage of the aortic (septal) cusp of the mitral valve in almost all patients with persistence of the ostium primum accounts for certain useful clinical findings. Second, we believe that this cleft, if unrecognized at operation, may account for the poor surgical results when such lesions are repaired in the same manner as other atrial septal defects. Both Rokitansky and Abbott assumed from the appearance of the valves that insufficiency had been present in life. Cahen et al.[38] demonstrated that the cleft mitral valve in one of their specimens at the time of autopsy was not competent to retain water introduced into the left ventricle. The degree of incompetence of the mitral valve due to the cleft probably is correlated with the severity of clinical signs and symptoms. Less frequently, other types of complexes associated with ostium primum may be unrecognized at operation. Surgeons should therefore not undertake the repair of ostium primum except by methods which permit direct observation and correction of the valvular abnormality.

Although the group of patients reported here is somewhat heterogeneous, consisting of cases of persistent common atrioventricular canal, ostium primum with cleft mitral valve, and incompletely diagnosed conditions associated with ostium primum, 10 clinical features were found to be characteristic of the group as a whole. Therefore, when all or most of these findings are present it should be possible to diagnose the presence of ostium primum. It is often impossible to distinguish between AV canal and ostium primum with cleft mitral valve preoperatively or before death at present. Possibly, with larger numbers of proved cases in the future, methods will be found for distinguishing between the various defects associated with ostium primum.

It is unnecessary to comment upon or enumerate the nonspecific symptoms and signs of congenital heart disease which were present in our cases as well as those in the literature. They have been mentioned in the case histories and are approximately the same as would be expected in any serious left-to-right shunt. The absence of Mongolism in any of our 14 patients is striking. This may be due to the fact that for the most part it is a series of surgical patients. Possibly Mongoloid children are less likely to come to surgery than children who are otherwise normal. Nevertheless, the fact that defects associated with ostium primum are not by any means limited to patients with Mongolism is worthy of emphasis. The lack of interest in the diagnosis of these conditions in the past may have been due to the misconception that they were to be found chiefly or only in those for whom the over-all prognosis was gloomy.

The physical findings are more suggestive of an interventricular than of an interatrial septal defect, because the murmur is loud and harsh and there is a thrill. The catheterization data will usually contradict such an impression, however. The apical systolic and diastolic murmurs with prolonged P-R interval and right ventricular hypertrophy on the electrocardiogram, the left-to-right shunt with left atrial enlargement on the x-rays, and arterialization in the atrium at catheterization have often led to the misdiagnosis of Lutembacher's syndrome.[13,38] Cahen et al.[38] refer to this picture as *faux syndrome de Lutembacher*. In our Case 1 an operation for mitral stenosis was done, but this condition was not found. Case 8 was also diagnosed as Lutembacher's syndrome by some observ-

ers. Such errors emphasize the fact that patients with defects associated with ostium primum have evidence of mitral disease, which is ascribable to insufficiency of the cleft septal cusp of the valve. Some confusion between mitral insufficiency and stenosis has been involved, however, since, so far as we are aware, none of the patients with ostium primum has had sound evidence of mitral stenosis. It is interesting that mitral systolic murmurs have even been reported in a case where surgical or pathological examination has shown isolated ostium primum without mitral cleavage.[26]

Although not pathognomonic, the pattern in the scalar electrocardiogram which gives the peculiar appearance of left axis deviation, horizontal position, and right ventricular hypertrophy is highly suggestive of an ostium primum type of lesion. Toscano-Barbosa et al.[53] have shown that the configuration may be explained by vectorcardiography, which often shows that the QRS loop in the frontal projection advances in a counterclockwise direction and is superior to the isoelectric point. They believe that the pathways of excitation into the ventricles are greatly altered by the anatomic defects. Manning and Taussig[49] interpreted the electrocardiograms in their cases of ostium primum with cleft mitral valve as showing left axis deviation with right and left ventricular hypertrophy. Three of our tracings (Cases 12 to 14) might be subject to this interpretation.

First degree AV block occurs more frequently in ostium primum than in other congenital anomalies. One may speculate that normally the interatrial septum plays a role in conducting impulses from the atrial musculature to the AV node at the crest of the interventricular septum. When an ostium primum is present, the part of the interatrial septum adjacent to the AV node is replaced by a hole, so that the atrial impulse must follow a devious course to reach it, and therefore atrioventricular conduction is delayed. Bailey et al.[1] have commented on the frequent appearance of complete AV block after surgery. It may be due to surgical trauma in the region of the AV node superimposed on a background of previously impaired conduction. Alteration of electrolytic, enzymatic, or other factors from normal may play some part as well.

The value of demonstrating left ventricular and left atrial enlargement may be appreciated when the roentgen findings are considered together with the catheterization data (see below), for if the latter show an interatrial left-to-right shunt, and enlargement of the two left-sided chambers is present, the lesion is much more likely to be ostium primum than one of the other types of interatrial defect. The chief cause of enlargement of the left-sided chambers in ostium primum is probably mitral insufficiency rather than shunt flow through the interventricular communication, since it was found in the cases of ostium primum with cleft mitral valve as well as in those with AV canal. The presence of an opening in the atrial septum, permitting escape from the left atrium into the right atrium of regurgitant flow from the mitral valve and shunt flow from the pulmonary veins, probably explains why the left atrial enlargement is of moderate degree.

When left-to-right shunts occur both between the atria and between the ventricles in defects associated with ostium primum, the malformation is more likely to be AV canal than ostium primum with cleft mitral valve, although this conclusion cannot be supported by our data, since the exact anatomical diagnosis is unknown in Cases 4 and 7. The important fact, however, is that interatrial left-to-right shunt alone may be found, as in Cases 2, 5, 9, and 10, where AV canal is known to be present. The reason that the interventricular shunt is often not detected is probably that there is already marked arterialization at the atrial level. The higher the oxygen saturation of the blood entering the right ventricle from the right atrium, the more admixture of fully saturated blood from the left ven-

tricle is necessary to produce a significant rise in oxygen content. Although the finding of pulmonary hypertension is not inconsistent with the diagnosis of interatrial septal defect other than ostium primum, the combination of interatrial left-to-right shunt and pulmonary hypertension should lead one to consider strongly the possibility of the presence of ostium primum, Lutembacher's syndrome, or an additional, undetected interventricular septal defect. In our cases the usual absence of arterial desaturation is confirmed; on the other hand, it should not be considered inconsistent with ostium primum lesions if present, especially in sick patients. We have not found atrial pressure tracings or the route that the catheter follows into the left side of the heart to be of much diagnostic value.

At present the differentiation of ostium primum with cleft mitral valve and persistent AV canal from most other types of congenital heart disease is usually possible by application of the 10 criteria listed above. The other conditions that are most difficult to distinguish from these two are Lutembacher's syndrome and interatrial defect other than ostium primum plus interventricular septal defect. We are not yet able to distinguish ostium primum with cleft mitral valve from AV canal unless catheterization shows arterialization in both the atrium and the ventricle, and we know very little about the findings in the numerous rarer combinations of lesions associated with ostium primum.

Summary and Conclusion

When there is abnormal development of the atrioventricular endocardial cushions in fetal life, there are four congenital cardiac lesions which may result—persistent ostium primum, cleavage of the aortic cusp of the mitral valve, cleavage of the septal cusp of the tricuspid valve, and deficiency of the membranous interventricular septum. About 11 different combinations of these lesions have been reported, and others may be possible. The most important combinations are persistent common atrioventricular canal, in which all four lesions are present, and ostium primum with cleft mitral valve.

An isolated ostium primum is rare. The presence of associated abnormalities, usually cleavage of the aortic cusp of the mitral valve, probably contributes greatly to the poor surgical risk in patients with this defect.

When an ostium primum is present, at least in ostium primum with cleft mitral valve and AV canal, a characteristic syndrome is produced which makes it possible to distinguish defects associated with ostium primum from other types of interatrial and interventricular septal defect.

The characteristic features are (*a*) a systolic thrill, (*b*) an apical systolic murmur, (*c*) diastolic murmurs, (*d*) prolonged P-R interval, (*e*) left axis deviation with right ventricular hypertrophy, (*f*) "horizontal heart" electrocardiographically, (*g*) left ventricular and (*h*) left atrial enlargement on x-rays, (*i*) interatrial shunt by catheterization, and (*j*) pulmonary hypertension.

At present it is not usually possible to distinguish the various complexes associated with ostium primum from one another prior to autopsy or operation.

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REFERENCES

1. Bailey, C. P.; Nichols, H. T.; Bolton, H. E.; Jamison, W. L., and Gomez-Almeida, M.: Surgical Treatment of 46 Interatrial Septal Defects by Atrio-Septo-Pexy, Ann. Surg. 140:805, 1954.

2. Lewis, F. J.; Varco, R. L., and Tauffic, M.: Repair of Atrial Septal Defects in Man Under Direct Vision with the Aid of Hypothermia, Surgery 36:538, 1954.

3. Rogers, H. M., and Edwards, J. E.: Incomplete Division of the Atrioventricular Canal with Patent Interatrial Foramen Primum (Persistent Common Atrioventricular Ostium), Am. Heart J. 36:28, 1948.

4. Méry: Mém. Acad. sc., 1700.

5. Ecker, A.: Beschreibung einiger Fälle von anomaler Communication der Herzvorhöfe und Bemerkungen über anomale Communication der

beiden Herzhälften überhaupt, deren Enstehung und deren Einfluss auf die Circulation, Inaugural Dissertation, Freiburg, 1839.

6. Peacock, T. B.: Malformation of the Heart Consisting in an Imperfection of the Auricular and Ventricular Septa, Tr. Path. Soc. London 1:34, 1846.

7. Reinhard, H.: Zur anatomischen und pathologischen Kentniss der dünnen Stelle in der Herzscheidewand (pars membranacea septi ventriculorum), Arch. path. Anat. 12:129, 1857, Case 3.

8. Hüter, C.: Grosse Communication zwischen beiden Vorhöfen unter dem verschlossenen Foramen ovale: Tod im 65. Lebensjahre, Arch. path. Anat. 30:587, 1864.

9. Tüngel, C.: Ein Fall von congenitaler zweifacher Perforation der Herzscheidewand: Tod durch Endocarditis und Embolie, Arch. path. Anat. 30:267, 1864.

10. Arnold, J.: Ein Beitrag zu der normalen und pathologischen Entwicklungsgeschichte der Vorhofsscheidewand des Herzens, Arch. path. Anat. 51:220, 1870.

11. Preisz, H.: Beiträge zur Lehre von den angeborenen Herzanomalien, Beitr. path. Anat. 7: 245, 1890.

12. Keith, A.: Malformations of the Heart, Lancet 2:433, 1909.

13. Planchu and Gardère: Un Cas de cyanose congénitale avec malformations cardiaques multiples chez un nourisson mort par endocardite infectieuse, Arch. méd. enf. 12:201, 1909.

14. Beattie, W. W.: Cardiac Anomaly (Bicameral Heart) in Situs Inversus, Internat. A. M. Museums Bull. 8:219, 1922.

15. Mönckeberg, J. G.: Das Verhalten des atrioventricularsystems bei persistierenden Ostium atrioventriculare commune, Zentralbl. allg. Path. 33 (Supp.):144, 1923.

16. Mönckeberg, J. G.: Die Missbildungen des Herzens, in Handbuch der speziellen pathologischen Anatomie und Histologie, edited by F. Henke and O. Lubarsch, Vol. 2, Berlin, Springer-Verlag, 1924, p. 40.

17. Schleussing, H.: Beiträge zu den Missbildungen des Herzens, Arch. path. Anat. 254:579, 1925.

18. Gunn, F. D., and Dieckmann, J. M.: Malformations of the Heart Including Two Cases with Common Atrioventricular Canal and Septum Defects and One with Defect of the Atrial Septum (Cor Triloculare Biventriculosum), Am. J. Path. 3:595, 1927.

19. Robson, G. M.: Congenital Heart Disease: A Persistent Ostium Atrioventriculare Commune with Septal Defects in Mongolian Idiot, Am. J. Path. 7:229, 1931.

20. von Rokitansky, C.: Die Defecte der Scheidewände des Herzens: Pathologisch-Anatomische Abhandlung, Wien, W. Braumüller, 1875.

21. Gellert, P.: Der Defekt im Septum primum atriorum des Herzens, Frankfürt. Ztschr. Path. 23:297, 1920.

22. Abbott, M. E.: Atlas of Congenital Cardiac Disease, New York, The American Heart Association, 1936.

23. Wakai, C. S., and Edwards, J. E.: Developmental and Pathologic Considerations in Persistent Common Atrioventricular Canal, Proc. Staff Meet. Mayo Clin. 31:487, 1956.

24. Campbell, M., and Missen, G. A. K.: Endocardial Cushion Defects: Common Atrio-Ventricular Canal and Ostium Primum, Brit. Heart J. 19:403, 1957.

25. Herxheimer, G.: Missbildungen des Herzens und der grossen Gefässe, in Schwalbe, E.: Die Morphologie der Missbildungen des Menschen und der Tiere, Jena, G. Fischer, 1910, Pt. 4, p. 339.

26. Allen, E. V., and Pruitt, R. D., Editors: Clinical Conference: A Diagnostic Problem; Noncyanotic Heart Disease with Heart Failure in a 7 Year Old Boy; A Clinical Pathological Conference Held at the University of Kansas Medical Center, Circulation 12:1924, 1955.

27. Blount, S. G.; Balchiem, O. J., and Gensini, G.: The Persistent Ostium Primum Atrial Septal Defect, Circulation 13:499, 1956.

28. Edwards, J. E.; Dry, T. J.; Parker, R. L.; Burchell, H. B.; Wood, E. H., and Bulbulian, A. H.: An Atlas of Congenital Anomalies of the Heart and Great Vessels, Springfield, Ill., Charles C Thomas, Publisher, 1954, p. 41.

29. Rogers, H. M.; Evans, I. C., and Domeier, L. H.: Congenital Aneurysm of the Membranous Portion of the Ventricular Septum: Report of 2 Cases, Am. Heart J. 43:781, 1952.

30. Abbott, M. E.: Congenital Cardiac Disease, in Modern Medicine: Its Theory and Practice, edited by W. Osler and T. McCrae, Ed. 3, Philadelphia, Lea & Febiger, 1927, Vol. 4, pp. 688 and 696.

31. Stahlman, M.; Kaplan, S.; Helmsworth, J. A.; Clark, L. C., and Scott, H. W.: Syndrome of Left Ventricular-Right Atrial Shunt Resulting from High Interventricular Septal Defect Associated with Defective Septal Leaflet of the Tricuspid Valve, Circulation 12:813, 1955.

32. Rogers, H. M., and Rudolph, C. C.: Persistent Common Atrioventricular Canal, Am. Heart J. 45:623, 1953.

33. Patten, B. M.: Human Embryology, Ed. 2, New York, The Blakiston Company (division of McGraw-Hill Book Company, Inc.), 1953, pp. 661ff.

34. Brandenburg, R. O., and DuShane, J. W.: Clinical Features of Persistent Common Atrio-

ventricular Canal, Proc. Staff Meet. Mayo Clin. 31:509, 1956.

35. Taussig, H. B.: Congenital Malformations of the Heart, New York, The Commonwealth Fund, 1947, p. 387.

36. Kaiser, A., and Schmid, F.: Die Herzfehlbildung bei Mongolismus, München. med. Wchnschr. 94:2167, 1952.

37. Moore, N.: Malformations of the Heart, Tr. Path. Soc. London 32:39, 1881.

38. Cahen, P.; Froment, R.; Gonin, A., and Traeger, J.: Faux syndrome de Lutembacher par persistence de l'ostium primum avec scission de la valve mitrale interne (complexe de Rokitanski-Maud Abbott), Arch. mal. coeur 45:203, 1952.

39. Rudolph, A. M.; Nadas, A. S., and Goodale, W. T.: Intracardiac Left-to-Right Shunt with Pulmonic Stenosis, Am. Heart J. 48:808, 1954.

40. Metianu, C.; Durand, M., and Heim de Balsac, R.: Persistence de l'orifice auriculo-ventriculaire, in Donzelot and D'Allaines: Traité des cardiopathies congénitales, Paris, Masson & Cie, 1954.

41. Watkins, E., Jr., and Gross, R. E.: Experiences with Surgical Repair of Atrial Septal Defects, J. Thoracic Surg. 30:469, 1955.

42. Jaffe, K.: Fall von Missbildung des Herzens und der Gefässe, Ztschr f. Anat. u. Entwcklngsgesch. 60:411, 1921.

43. Reineboth: Die Entstehung des Venenpulses bei Communication der Vorhöfe und gleichzeitiger Insufficienz der Mitralis, Deutsche med. Wchnschr. 21:870, 1895.

44. Leech, C. B.: Congenital Heart Disease: Clinical Analysis of 75 Cases from The Johns Hopkins Hospital, J. Pediat. 7:802, 1935.

45. Ash, R.; Wolman, I. J., and Bromer, R. S.: Diagnosis of Congenital Cardiac Defects in Infancy: A Study of 32 Cases with Necropsies, Am. J. Dis. Child. 58:8, 1939.

46. Curtin, J. Q.: Congenital Cardiac Anomaly: Persistent Common Atrioventricular Ostium, Am. Heart J. 44:884, 1952.

47. Braudo, J. L.; Nadas, A. S.; Rudolph, A. M., and Neuhauser, E. B. D.: Atrial Septal Defects in Children: A Clinical Study with Special Emphasis on Indications for Operative Repair, Pediatrics 14:618, 1954.

48. Edwards, J. E.; Dry, T. J.; Parker, R. L.; Burchell, H. B.; Wood, E. H., and Bulbulian, A. H.: An Atlas of Congenital Anomalies of the Heart and Great Vessels, Springfield, Ill., Charles C Thomas, Publisher, 1954, p. 41.

49. Manning, J. A., and Taussig, H. B.: The Clinical Syndrome of Persistent Ostium Primum, read by title before the American Pediatric Society, June, 1955.

50. Kjellberg, S. R.; Mannheimer, E.; Rudhe, U., and Jonsson, B.: Diagnosis of Congenital Heart Disease, Chicago, The Year Book Publishers, Inc., 1955, p. 359.

51. Robinson, D. W.: Persistent Common Atrioventricular Ostium in a Child with Mongolism, Arch. Path. 32:117, 1941.

52. Moragues, V.: Persistent Common Atrioventricular Ostium: Report of a Case, Am. Heart J. 25:123, 1943.

53. Toscano-Barbosa, E.; Brandenburg, R. O., and Burchell, H. B.: Electrocardiographic Studies in Cases with Intracardiac Malformations of the Atrioventricular Canal, Proc. Staff Meet. Mayo Clin. 31:513, 1956.

54. Harned, H. S., Jr.; Crothers, C. H., and Whittemore, R.: Diagnosis of Atrial and Ventricular Septal Defects, Am. J. Dis. Child. 90:211, 1955.

55. Wakai, C. S.; Swan, H. J. C., and Wood, E. H.: Hemodynamic Data and Findings of Diagnostic Value in 9 Proved Cases of Persistent Common Atrioventricular Canal, Proc. Staff Meet. Mayo Clin. 31:500, 1956.

56. Swan, H. J. C.; Burchell, H. B., and Wood, E. H.: The Presence of Venoarterial Shunts in Patients with Interatrial Communications, Circulation 10:705, 1954.

57. Disenhouse, R. B.; Anderson, R. C.; Adams, P., Jr.; Novick, R.; Jorgens, J., and Levin, B.: Atrial Septal Defect in Infants and Children, J. Pediat. 44:269, 1954.

CORRECTION

In the article "Sickle-Cell Anemia in Infancy," by Sanford L. Leikin, M.D., and James W. McCoo Jr., B.S., in the July issue of the JOURNAL, it was stated in a footnote at the bottom of page 51 that Mrs. Lily Singer, of the Department of Hematologic Research, The University of Chicago, performed the Tiselius electrophoresis. Mrs. Singer is a member of the Department of Hematologic Research of the Michael Reese Hospital, Chicago.

Abstracts from Current Literature

American Journal of Pathology, Ann Arbor, Mich.

Abstracted by Jay Bernstein, M.D.

34, No. 2 (March-April) 1958

The Morphology of Clubbing. F. Calvin Bigler.—p. 237.
Alterations in the Dorsal Root Ganglia and Adjacent Nerve in the Leukemias, the Lymphomas and Multiple Myeloma. Robert C. Dickenman and J. L. Chason.—p. 349.
* Idiopathic Demyelinating Disease in Youth: A Study of Three Cases. Lawrence J. McCormack.—p. 375.

Idiopathic Demyelinating Disease in Youth: A Study of Three Cases.—Three cases of fatal demyelinating disease occurred on young males, and in two of them there were accumulations of birefringent crystals which were lipid in nature. The histologic appearance of these two cases was similar to that of disseminated sclerosis and was difficult to distinguish from that of diffuse sclerosis. The author expressed the opinion that the pathologic process was closely related to disseminated sclerosis in that the unidentified lipid reflected a pathway of myelin breakdown.

American Journal of Roentgenology, Radium Therapy and Nuclear Medicine, Springfield, Ill.

Abstracted by Donald H. Altman, M.D.

78 (Oct.) 1957

* Gastrointestinal Manifestations of the Schönlein-Henoch Syndrome: Roentgenologic Findings. Jack Handel and Solomon Schwartz.—p. 643.
* The Use of Water Soluble Contrast Medium (Hypaque) for Gastro-Roentgenography. Bernard S. Epstein.—p. 694.

Gastrointestinal Manifestations of the Schönlein-Henoch Syndrome: Roentgenologic Findings.—The Schönlein-Henoch syndrome is characterized by nontraumatic hemorrhagic diathesis with bleeding into the joints, skin, viscera, or any combination of these. The article reports two cases, and the radiographic picture of involvement of the small bowel is presented. These two cases are in adults, but previous reports on this disorder have stated that approximately 48% of the cases occur in children. None have been reported in which the infant is younger than 2 years of age. The disorder possibly represents an allergic manifestation, and the pathology appears to be the same observed in polyarteritis except for the fact that in polyarteritis the changes are within the arteries and this disorder reveals changes in the capillaries. The changes within the arterioles are common to both.

The clinical manifestations of purpuric exanthem, visceral hemorrhage, and joint symptoms are discussed. The fact that this disorder may present itself as acute abdominal pain prior to manifestation of the cutaneous disorder and the fact that radiographic findings may occur prior to manifestation of skin lesions are noted. The radiographic changes in the bowel appear to occur exclusively in patients who have gastrointestinal bleeding. Apparently, increased capillary fragility is responsible for extravasation of serosanguineous fluid into the intestinal wall, with edema of the mucosa and submucosa. There is relatively high incidence of intussusception, apparently occurring as extravasation of blood causes local paresis and interruption of peristaltic waves, permitting invagination of the uninvolved proximal segment into the paretic segment.

The Use of Water Soluble Contrast Medium (Hypaque) for Gastro-Roentgenography.—This article is of interest in pediatrics, as the use of water-soluble contrast media offers certain definite advantages in gastrointestinal radiography. This material is now available in powdered form and can be readily converted into any desired concentration. The only significant untoward effect was a tendency to mild diarrhea. One patient with known allergies had hives, which disappeared after an antihistamine was given by mouth.

In infants and young children the material was diluted to approximately 25% solution. The demonstration of the mucosal pattern of the stomach was adequate. It appeared as if

good mucosal patterns of the small bowel were not obtained with the aqueous medium. The medium is also of value in barium enemas.

American Review of Tuberculosis and Pulmonary Diseases, New York

Abstracted by Edwin L. Kendig Jr., M.D.

77, No. 3 (March) 1958

The Hazards of Radiation. David M. Gould and Walter Mauderli.—p. 375.
Tuberculosis in the Neonatal Period. Edwin L. Kendig Jr. and William L. Rodgers.—p. 418.
A Study of the Growth in HeLa Cells of Tubercle Bacilli from Human Sputum.—C. C. Shepard.—p. 423.
Tissue Culture Studies on Resistance in Tuberculosis: I. Normal Guinea Pig Monocytes with Tubercle Bacilli of Different Virulence. Morgan Berthrong and Mary Alice Hamilton.—p. 436.
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* The Detection of Antibodies in the Serum of Tuberculous Patients by an Agar Double-Diffusion Precipitation Technique. Robert C. Parlett, Guy P. Youmans, Caroline Rehr, and William Lester.—p. 462.
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Biologic and Biochemical Activities of "Cord Factor," with Special Reference to Its Role in the Virulence of Tubercle Bacilli. Masahiko Kato, Katsuji Miki, Kiyoteru Matsunaga, and Yuichi Yamamura.—p. 482.
Acute and Anaphylactic Shock Due to Para-Aminosalicylic Acid. H. P. B. Harvey and H. J. Solomon.—p. 492.
A Rapid Means of Differentiating Atypical Acid-Fast Bacilli and Avian Tubercle Bacilli from Other Mycobacteria: The Neotretrazolium Inhibition Test. Mireille Gastambide-Odier and D. W. Smith.—p. 662.
Differentiation of Human Tubercle Bacilli from Atypical Acid-Fast Bacilli: I. Niacin Production of Human Tubercle Bacilli and Atypical Acid-Fast Bacilli. Kiyoshi Konno, Rudolf Kurzmann, Kenneth T. Bird, and Anthony Sbarra.—p. 669.
* Differentiation of Human Tubercle Bacilli from Atypical Acid-Fast Bacilli: II. Clinical Application. Kiyoshi Konno, Rudolf Kurzmann, Kenneth T. Bird, and Anthony Sbarra.—p. 675.
Lung Density as a Measure of Tuberculous Involvement in Mice. Alfred J. Crowle.—p. 681.
The Chemotherapeutic Activity upon Chromogenic Mycobacteria of Certain Derivatives of Thiocarbanilide (Su 1906), Thiazoline (Su 3068), and Thiazolidinone (Su 3912). R. L. Mayer, P. C. Eisman, T. A. Gisi, and E. A. Konopka.—p. 694.
The Antituberculous Activities of Substituted Thiazolines and Thiazolidinones. P. C. Eisman, E. A. Konopka, T. Gisi, R. H. Mizoni, and R. L. Mayer.—p. 703.
The Chemical Constituents of Mycobacterium Paratuberculosis. A. B. Larsen and R. S. Merkal.—p. 712.
Sputum Examination Following Bronchoscopy: Its Significance in Tuberculosis. E. G. Laforet and J. W. Strieder.—p. 716.
Antituberculous Vaccination in the Guinea Pig with Non-Living Vaccines. David W. Weiss.—p. 719.

The Detection of Antibodies in the Serum of Tuberculous Patients by an Agar Double-Diffusion Precipitation Technique.—The authors present the results obtained through the use of a modified double-diffusion precipitation method for the detection of antibodies against mycobacterial antigens in the serum of clinically well persons and in the serum of persons suffering from tuberculosis and leprosy. The antigens employed were concentrated filtrate preparations of cultures of Mycobacterium tuberculosis var. hominis, strain H37Rv, the saprophytic mycobacterial strain 607, Nocardia pelliteriae, Penicillium notatum, and Candida albicans.

In tests of the serum of 53 patients, all but 4 possessed antibodies which reacted only with the antigens present in the concentrated culture filtrate of the H37Rv culture of Mycobacterium tuberculosis var. hominis. Of the four negative specimens of serum, three came from subjects who did not have tuberculous disease and one came from a patient with pulmonary disease caused by an atypical acid-fast micro-organism which was antigenically related to Mycobacterium ulcerans. Antibodies specific for M. ulcerans were found in the serum of this patient.

Sera from 38 clinically well persons, who had a positive reaction in the Mantoux test (1:5000 or 1:100 dilution O. T.) at the time the blood sample was drawn, were also tested. In only two instances were antibodies against mycobacterial antigens found. One of these two whose serum gave a positive test had had a tuberculous kidney removed 11 months previously. The other, a graduate student who had worked with cultures of virulent tubercle bacilli in the labratory for a period of several months, showed no evidence of active disease.

Sera from 13 patients with leprosy showed no antibodies.

Differentiation of Human Tubercle Bacilli from Atypical Acid-Fast Bacilli: II. Clinical Application.—In an accompanying study, the authors pointed out a marked difference in the amount of niacin produced by human tubercle bacilli compared with the niacin production of atypical acid-fast bacilli. In the present article, the production of niacin was

used as an index and two studies were carried out: 1. Of the 26 unknown strains of the Sunmount Cooperative Study, 3 were correctly indentified as human tubercle bacilli and the remaining 23 strains were found to be other strains of mycobacteria. 2. Six hundred sixty-three routine tuberculosis hospital cultures, classified as tubercle bacilli in their respective laboratories, were studied. Of these, six strains were identified as mycobacteria other than human tubercle bacilli and one strain was found to be Nocardia.

Archives of Diseases in Childhood, London

Abstracted by R. Janet Watson, M.D.

32, No. 166 (Dec.) 1957

The Treatment of Oesophageal Atresia. Einar Sandegärd.—p. 475.
* Hepatic Haemorrhage in the Newborn. J. J. Mason Brown.—p. 480.
Traumatic Intramural Haematoma of the Proximal Jejunal Loop.—F. H. Robarts.—p. 484.
Head Injuries in Childhood. Philip Harris.—p. 488.
Injuries Involving the Teeth and Jaws in Young Children. W. Donald MacLennan.—p. 492.
The Prevention of Accidents in Childhood in Sweden. T. Ehrenpreis.—p. 495.
Community Aspects of Trauma in Childhood. J. H. F. Brotherston.—p. 499.
The Resuscitation of Burned Children. A. D. R. Bathelor.—p. 502.
* Spontaneous Dislocation of the Cervical Spine in Childhood. R. M. I. Mackay.—p. 505.
The Surgery of Premature Infants. P. P. Rickham.—p. 508.
The Pathology of Congenital Ring Constrictions. Denis Browne.—p. 517.
A Treatment of Undescended Testicle in Infancy.—C. G. Scorer.—p. 520.
Bacteroides Infection in the Surgery of Childhood. A. A. Gunn.—p. 523.

Hepatic Haemorrhage in the Newborn.—The author reviews the literature and gives one case report. Hepatic hemorrhage was the direct cause of death in from 1.2% to 5.6% of stillbirths and neonatal deaths. The liver was the source of intra-abdominal hemorrhage in 39% and 32% of cases in two different series. The author's case was an infant weighing 11 lb. 4 oz.; the mother was delivered with difficulty, and on the 4th day of life the infant was pale and lethargic. Hemoglobin was 50%, and the x-ray of the abdomen showed the presence of fluid. At laparotomy there was a very large ruptured supcapsular hematoma on the anterior surface of the liver. A laceration of the liver was sutured. Over 350 cc. of blood was removed from the peritoneal cavity, and the baby was transfused rapidly with 400 cc. of blood. The infant made a rapid and uneventful recovery.

Spontaneous Dislocation of the Cervical Spine in Childhood.—The author reports 10 cases of spontaneous dislocation of the cervical spine occurring in children ranging in age from 1½ to 10 years. The dislocations were associated with cervical adenitis or nasopharyngitis and occurred from one day to three weeks after admission to the hospital. All were corrected by treatment with hyperextension. None had any neurological complications.

Canadian Medical Association Journal, Montreal

78, No. 6 (March 15) 1958

Abstracted by H. M. Keith, M.D.

Bee Sting Allergy and Desensitization: A Report of Cases and Review of the Literature. Frank W. Schofield.—p. 412.
Myelogenous Leukemia in A Stillborn Infant. Georgina R. Hogg. and Otto A. Schmidt.—p. 421.

Circulation, New York

17, No. 3 (March) 1958

Abstracted by Anthony C. Nolke, M.D.

Infradiaphragmatic Total Anomalous Pulmonary Venous Connection. Arnold L. Johnson, F. W. Wiglesworth, J. S. Dunbar, Sarjit, Siddoo, and Maria Grajo.—p. 340.
Coexistence of Patent Ductus Arteriosus and Congenital Aortic Valvular Disease. Herbert Mark, Belle Jacobson, and Dennison Young.—p. 359.
Bronchial Obstruction Due to Pulmonary Artery Anomalies: I. Vascular Sling. Stephen Contro, Robert A. Miller, Harvey White, and Willis J. Potts.—p. 418.
Bronchial Obstruction Due to Pulmonary Artery Anomalies: II. Pulmonary Artery Aneurysm. Stephen Contro, Robert A. Miller, Harvey White, and Willis J. Potts.—p. 424.

Abstracts for the Soviet Literature

A selection of abstracts drawn from the current issue of Abstracts of Soviet Medicine, *a quarterly journal published by the Excerpta Medica Foundation (New York Academy of Medicine Building, 2 E. 103d St., New York 29), with the aid of a grant from the U. S. Public Health Service*

Newborn Period, Prematurity, Embryopathy

Morbid anatomy of congenital toxoplasmosis K voprosu o patologicheskoi anatomii vrozhdennogo toksoplazmoza. IVANOVSKAYA T. E. and SEMENOVA K. L. Department of Morbid Anatomy of the Children's Hospital no. 1, Moscow *Arkh. Pat.* 1956, 18/7 (92-100) Illus. 11 Ref. 15.

The morphological changes found in the CNS and internal organs of newborn infants with congenital toxoplasmosis are described. Obvious signs of the disease in mothers were absent. In the cases of congenital toxoplasmosis numerous foci of necrosis were found in the gray and white matter of the cerebral hemisphere. Important factors in the causation of the necrosis are alterations in permeability of the vessel walls and the indirect action of the pathogenic agent on the cerebral tissues. The morphology of the disease depends on the severity of the disorder as well as on the existence of necrotic foci. Signs of productive inflammation predominated during the acute stage; the brain tissue was replaced by granulation tissue in which spherical colonies of the pathogenic agent were found. In processes of long duration and involving smaller areas the dominant feature is resorption of the necrotic foci with formation of cystic cavities and fissures filled with granular spheres, between which the terminal colonies of the parasite could be found. The morphological variations described determine the clinical manifestations of the disease. The productive inflammation gives the picture of meningoencephalitis, and the resorptive processes give the picture of defective development of the CNS. Where the inflammatory changes are predominant, congenital toxoplasmosis may have the character of a generalized septicemia with inflammatory interstitial changes in the parenchymatous organs. The authors consider that in many cases defective development of the CNS (microcephaly, anencephaly) and of the eyes in children is caused by congenital lesions of the CNS due to toxoplasmosis.

Cardiovascular System

Current problems of heart surgery in children Aktualnye voprosy khirurgii serdtsa v detskom vozraste. PETROVSKII B. V. *Sovet. Med.* 1956, 8 (8-17).

Diagnostic and surgical problems of the heart in children are discussed. Intratracheal narcosis was employed, and the operation carried out during a hypothermic state. To prevent complications blood transfusions (intravenous and intraarterial) and infusions of glucose and physiologic solution were employed. Great care was taken postoperatively to prevent cerebral oedema. One hundred ten children were operated on with various congenital and acquired heart conditions, including adhesive pericarditis following rheumatic fever. The results were good. The operation was done on five children (13 to 15 years of age) with mitral stenosis of rheumatic etiology. The results were better than in adults.

Mechanisms of compensation in the lesser circulation in congenital combined cardiac defect of the cyanotic type with good function of the bulbus cordi (tetralogy of Fallot) K mekhanizmam kompensatsii malogo kruga krovoobrashcheniya pri kombinirovannykh vrozdennykh prokakh serdtsa tsianoticheskogo tipa s pravodelennostyu bulbusa serdtsa (tetrada Fallot). ARKHANGELSKAYA N. V. Surgical Faculty Clinic of the Pirogova Second Medical Institute, Moscow *Arkh. Patol.* 1956, 18/7 (65-73) Illus. 9 Ref. 30.

The characteristics of the intrapulmonary circulation in congenital heart defects (Fallot's tetralogy) and the compensating action of the bronchial vessels were studied. The lungs of 50 deceased subjects aged 3 to 25 years who had suffered from this cardiac defect were examined. Morphological methods, roentgenangiography, and a corrosion technique were used. It was found that, in combined congenital cardiac defects of cyanotic type with good function of the bulbus cordi, the functionally insufficient blood supply of the lungs is compensated by the development of a wide network of anastomoses between the vessels of the greater and the lesser circulation. The bronchial essels become dilated and tortuous. Hypertrophy of the muscular layer of the walls and hyperplasia of elastic elements is observed. Numerous anastomoses develop between the peripheral branches of the bronchial and pulmonary arteries and also between the pulmonary arterial and venous mesh of the bronchi. The supply of blood to the pul-

monary artery is increased through these routes, and improved conditions for drainage are also created.

Organization of centers for treatment of angiomas in children with carbon-dioxide snow in the district hospitals Organizatsiya punctov lecheniya angiom u detei snegom ugolnoi kisloty v usloviyakh raionnykh bolnits. MYACHIKOV B. V. *Pediatriia* 1956, 6 (69-71).

In view of the great importance of timely treatment of angiomas in children of young age, the author recommends that the treatment of angiomas should be organized in district hospitals. The method of treatment consists in obtaining freezing of second degree of the skin overlying the tumor by pressing a lump of carbon dioxide for 15 to 35 seconds, using moderate pressure. The number of applications varies from 2 to 3 to 10 to 15, depending on the size and localization of the angioma. Subsequent applications are given after subsidence of the inflammatory reaction from the previous application, i. e., after 7 to 10 days. The duration of subsequent applications is increased by 3 to 5 seconds, since the sensitivity of the cutaneous covering undergoes a change.

Gastrointestinal System

Investigation of gastric secretion by the Bykov-Kurtsin method Issledovanie zheludochnoi sekretsii metodom Bykova-Kurtsina. KOSSYURA M. B. *Pediatriia* 1956, 6 (3-10).

Gastric secretion was studied by the Bykov-Kurtsin method in 47 children (mostly of school age) who were admitted with abdominal pains. These children suffered from various diseases of the gastorintestinal tract: hepatocholecystitis, chronic colitis and enterocolitis, tapeworm infestation, etc. The investigation of gastric juice lasted 2½ hours. A double tube with an inflatable rubber balloon was introduced into the stomach, and a Krasnogorskii's cap with a rubber tube for collecting saliva was applied to the parotid duct. After the evacuation of all the fasting gastric juice, the balloon was inflated with 150 to 200 ml. of air and four samples of gastric contents were extracted by means of four to six aspirations with a syringe. At the end of one hour the air was removed and a 7% cabbage broth (150 ml.) was introduced as a chemical stimulus. Thereafter, 10 ml. of gastric contents was removed at 15-minute intervals, and the remaining gastric contents were removed at the end of 1½ hours. The size of the second portion (after the introduction of cabbage broth) is a measure of the emptying function of the stomach, and the last four portions, a measure of the "neurochemical phase." The Bykov-Kurtsin method makes it possible to establish the character of the secretion in its various phases (complex reflex and neurochemical) and to correctly evaluate the entire secretory process, as well as the emptying function of the stomach.

Characteristics of the functional state of the nervous system in older children with diseases of the alimentary tract K kharakteristike funktsionalnogo sostoyaniya nervnoi systemy u detei starshego vozrasta s zabolevaniyami pishchevaritelnogo apparata. KOSSYURA M. *Pediatriia* 1956, 5 (28-35).

An investigation was carried out on 62 children of 3 to 15 years of age with peptic ulcer, gastritis, intestinal infantilism, hepatocholecystitis, chronic hepatitis, and some other conditions. The general condition was satisfactory in nearly all cases. The state of higher nervous activity was judged by the author on the basis of a detailed historical study of the development of the child's nervous system from birth. Other points taken into account were the child's reaction to his disease, his reactions to environmental stimuli, and especially his behavior at school, in his home, and in the clinic. The children were divided into three groups: (*a*) those with the predominance of excitation processes, (*b*) those with the predominance of inhibitory processes, and (*c*) those with adequately balanced basic nervous processes. The functions of the vegetative compartment of the CNS were studied on the gastric and unconditioned salivary secretions. The author observed more or less marked disturbances of the vegetative compartment of the CNS in the majority of the children, depending on the form and severity of disease. Moreover, in a number of children with predominance of either excitation or inhibition considerable disturbances of the vegtative indices were observed, irrespective of severity of the disease. This points to a dependence of these indices on the state of higher nervous activity. Similar relations either to the character of the disease or to the functional state of the CNS were revealed during the study of the unconditioned salivary secretion and of gastric secretion. In a proportion of children an improvement followed a change of environment with establishment of a proper mode of living. This points to the importance of the state of higher nervous activity in the development of certain gastrointestinal diseases.

Intestinal enzymes in acute gastrointestinal diseases of infants Kishechnye fermenty pri ostrykh zheludochno-kishechnykh zabolevaniyakh detei rannego vozrasta. DILIGENSKAYA L. A. and VALTER E. M. *Pediatriia* 1956, 5 (35-39).

The authors investigated the phosphatase and enterokinase content in fresh (not later than two hours after defecation) feces of children. Enzymatic activity was calculated in arbitrary units per 1 gm. of the material. Since normal values for the feces of children had not yet been established, a preliminary investigation was carried out in healthy infants. It was found that in the majority of children phosphatase activity varied between 1000 and 5000 units and enterokinase activity, between 1000 and 2250 units. These figures were provisionally regarded as the normal limits. The content of intestinal enzymes was then estimated in 100 children aged from 3 weeks to 2 years, with acute gastrointestinal conditions, viz., simple dyspepsia, in 42 cases; toxic dyspepsia, in 14, and parenteral dyspepsia, in 44. Changes in activity of the enzymes were noted not only in acute gastrointestinal diseases but also in respiratory diseases, even in the absence of dyspeptic phenomena. There was some dissimilarity in the changes which enterokinase and phosphatase underwent during acute gastrointestinal disturbances. A reduction in enterokinase content was noticed even during the first days of the disease, especially in toxemic dyspepsias. A drop in phosphatase, on the other hand, was generally observed as the disease progressed; with recovery, the phosphatase tended to return to a mean level. In other words, enterokinase, as a truly intestinal ferment, suffered to a greater extent. In "parenteral dyspepsias" the dynamics of the intestinal enzymes were more or less the same. The authors underline the fact that in children suffering from dyspepsias enzymatic activity generally fluctuates within the same limits as in the control group, but the amplitude of these fluctuations is greater depending on the patient's condition as well as on the form and duration of the disease.

Respiratory System

Treatment of pneumonia in young children Lechenie pnevmonii u detei rannego vozrasta. TUR A. F. *Sovet. Zdravookhr. Kirgizii* 1956, 5 (10-14).

The author advises against taking a child with pneumonia directly out of doors; on frosty days, it is better to take a walk inside the building. Humid oxygen should be given for up to 15 to 20 minutes at short intervals. Antibiotics are indicated for 10 to 12 days, starting with 20,000 to 30,000 units of penicillin per kilogram of body weight. Sometimes a combination of two or, rarely, three, antibiotics may be expedient. After antibiotic treatment sulfonamides should be given for a short time.

Use of ecmonovocillin (preparation of penicillin) as prophylactic against pneumonia in acute upper respiratory tract catarrh and influenza in children Primenenie ekmonovotsillina v tselyakh profilaktiki pnevmonii pri ostrom katare verkhnikh dykhatelnikh putei i grippe u detei. SHPIRT YA. YU. and LAVROVA E. V. *Antibiotiki* 1956, 16 (34-36).

Ecmonovocillin was given i. m. to 106 children suffering from influenza and upper respiratory tract catarrh. Through the first three days of illness doses of 100,000 units were given to children below 2; those over 2 had 150,000 unit doses for 24 to 36 hours until the temperature fell. Forty-seven children received two injections each. In a control group of 228 children, treatment given was sulfathiazole with or without penicillin. Among children treated with Ecmonovocillin 2 cases of pneumonia were recorded, while among the control children there were 26 cases of pneumonia. The authors consider that Ecmonovocillin effectively prevents pneumonia in infants and children suffering from influenza and acute upper respiratory tract infection.

Virological and morphological features of influenzal pneumonia in early childhood Virusologicheskaya i morphologicheskaya kharakteristika grippoznikh pnevmonii w rannem detskom vozraste. MAKSIMOVICH N. O., KORNYUSHENKO N. P., VOTSMAN N. E., and YATEL T. P. *Pediat. Akush. i Ginek.* 1956, 5 (14-20).

It is believed that newborns, owing to passive immunity, do not contract virus influenza. The authors consider that there is a low level of antibodies against influenza in the newborn. Thirty-four cases of infants who died of pneumonia during an outbreak of influenza were investigated. Virological examination of the lung tissue and of the upper respiratory tract revealed influenzal virus in seven cases. In nine cases clinical pathological findings could not exclude influenza as the etiological factor. The illness lasted on average two to five days, with high temperature, cough, rapid development of toxemia, adynamia, loss of consciousness, convulsions, cyanosis, and dyspnea. Hypothetically a clinical diagnosis of influenzal pneumonia

was, however, made only in six cases. Microscopic examination of the lungs of infants who succumbed in the first few days of the disease revealed interstitial hemorrhages, congestion, epthelial metaplasia, and formation of intra-alveolar membarnes, interfering with gaseous exchange, producing anozemia. Necrotizing bronchitis with peribronchitis appeared at a later stage. The authors point to the role of influenza as an important causative agent of toxic pneumonia in infants.

Surgical treatment of purulent lung diseases in children Khirurgicheskoe lechenie khronicheskikh gnoinykh zabolevanii legkikh u detei. DBEIKOVSKAYA E. G. *Khirurgiia* 1956, 10 (36-41).

Endocrine System

Brephoplasty of glands of internal secretion Brefoplastika zhelez vnutrennei sekretsii. KADYSEVA N. M. Medical Institute, Yaroslavl *Probl. Endokr.* 1956, 2/6 (90-98).

The treatment of four patients with pituitary dwarfism by means of transplantation of the pituitary from human fetuses at the fifth to the sixth month of pregnancy is described. The pituitary transplantation was performed on the day the fetus was delivered and was performed in the thickness of the abdominal rectus muscle. A detailed account is given of one case of pituitary dwarfism under observation over a period of 20 years. In the course of this period three pituitary transplants were performed (in 1936, 1950, and 1952). The patient increased in height from 114 cm. to 151 cm. and showed normal sexular development. Blood transfusion, particularly of the blood of pregnant women, promotes more vigorous growth.

Syndrome of diabetes mellitus in the so-called renal glycosuria found in a child aged 6 Sindrom sakharnogo diabeta pri tak nazyvaemoi pochechnoi glyukozurii u rebenka 6 let. KRAINOVSKAYA F. M. *Pediat. Akush. i Ginek.* 5 (28-32).

The pathogenesis of renal glycosuria is obscure. Some authors believe that it has no connection with diabetes, and others maintain that renal glycosuria sooner or later changes into diabetes mellitus. In this paper the history is given of a girl aged 5½ diagnosed as having diabetes mellitus (pancreatic), caused possibly by epidemic parotitis. The child was under observation for over two years. She recovered, but a tendency to renal glycosuria persisted. The author regards renal glycosuria as being possibly a prediabetic condition changing eventually into diabetes. He therefore draws the attention of all pediatrists to prediabetic conditions, so that by early treatment diabetes might be averted.

Some remote sequelae of epidemic kepatitis in children Nekotorye otdealennye posledstiviya bolezni Botkina u detei. IVANOVA E. M. *Pediat. Akush. i Ginek.* 1956, 6 (13-18).

One hundred four children who had epidemic hepatitis were kept under observation for one to two years and longer. In many children exacerbations and recurrences of the disease appeared at different times after discharge; the causes were dietary indiscretions, overexertion, and intercurrent illnesses. For a long period after discharge disturbances of the secretory function of the stomach were noticed. Four groups of children could be distinguished in the course of the observations: (1) practically healthy children, (2) those with manifestations of an inactive hepatitis, (3) those with symptoms of chronic hepatitis, and (4) children in whom the disease progressed to cirrhosis of the liver. These data point to the necessity of early hospitalization in the acute stage of the disease and of a treatment carried on to completion and of a prolonged period of observation of convalescents with a thorough laboratory investigation. Children in the acute stage of epidemic hepatitis must be hospitalized early and treated systematically.

The follow-up history of children who have had epidemic hepatitis Katamnez detei, perenesshikh bolezn Botkina. KULIK L. M. *Pediat. Akush. i Ginek.* 1956, 6 (18-22).

Many liver diseases in children are connected with an earlier incurred epidemic hepatitis; in only 6 out of 60 children did the author establish a clinical cure; the remainder showed residual changes, transition to chronic hepatitis, and cirrhosis of the liver with development of Banti's syndrome. In the follow-up examinations of children the following changes were noted in the nervous system: the appearance of lesions caused by toxemia, with radicular and polyneuritic syndromes, focal lesions, a syndrome of CSF hypertension, and a disordered tonus of the autonomic nervous system. Frequently the functions of detoxicating and of carbohydrate and pigment metabolism were impaired. The detection of a latent functional liver insufficiency is very important. Frequent causes of deterioration are intercurrent illnesses, dietary indiscretions, etc. The sequelae of epidemic hepatitis as revealed by the follow-up investigations make hospitalization necessary even in cases of mild forms of the

disease, with institution of a comprehensive therapeutic schedule, a thorough clinical and biochemical investigation, and a prolonged outpatient observation of the patients.

Congenital atresia of esophagus Vrozhdennaya neprokhodimost pishchevoda. KOSSAKOVSKII Y. *Khirurgiia* 1956, 10 (11-17).

Exact diagnosis of esophageal atresia is possible only by roentgenologic examination. Symptoms are observed in the first days of the infant's life: salivation from the corners of the mouth, regurgitation of fluids, and impossibility to pass a rubber tube into the stomach. In such children immediate surgical intervention is imperative as the only procedure capable of saving the infant's life. Thorough aspiration of the bronchia secretions is necessary before operation with intratracheal anesthesia. The most convenient operative approach is via the fifth right intercostal space; after the operation a gastrostomy is established for feeding. Individual postoperative nursing care includes administration of oxygen, carrying around in the arms, and careful aspiration of pharyngeal secretions every 7 to 10 minutes during the early days. Cyanosis and increasing dyspnea call for immediate aspiration of bronchial secretions. Peroral feeding may be commenced on the 10th to 12 day. After a successful operation careful observation for several months is necessary for early recognition of scar stricture at the site of anastomosis.

Three cases of clinically diagnosed left diaphragmatic hernia in the newborn Tri sluchaya raspoznannoi pri zhizni levostronnei diafragmalnoi grizhi u novorozhdennikh detei. DBROVSKAYA N. A. *Sovet. Zdravookhr. Kirgizii* 1956, 5 (64-65).

The cases were diagnosed by x-ray examination with barium.

Pathogenesis of chronic nonhealing fistulae arising in the soft tissues in children after injections of penicillin, anatoxin, and other medicinal substances K voprosu o patogeneze dlitelno ne zazhivayushchikh svishchei, voznikshikh u detei v myagkikh tkanyakh posle inektsii penitsillina, anatoxina i drugikh lekarstvennykh veshchestv. SOBOLEVA N. I. and EREMEEVA A. S. *Arkh. Pat.* 1956, 18/7 (126-131).

The authors observed nonhealing fistulae in the soft tissues in 50 children following introduction of penicillin and other therapeutic substances. At the site of inoculation, especially after the first injection, a nonabsorbable firm infiltrate appeared, and later a fistula formed. Attempts at conservative and surgical treatment (a simple opening up of the infiltrate) remained unsuccessful. Only a radical excision, within the limits of healthy tissue, after the method suggested by S. D. Ternovskii, made it possible to rid children of such a severe malady. Histological investigation of the material makes it possible to establish a connection between the pathogenesis of the above-described complications, the generally changed reactivity of the child's organism, and the local allergic state of the tissues.

Method of sternal puncture in childhood K voprosu o metodike punktsii grudiny v detskom vozraste. AVTSEN S. B. *Pediatriia* 1956, 6 (27-29).

To solve the controversial problem as to which part of the sternum in children should be used for puncture, the author carried out 2200 measurements of the sternum on cadavers of children in the neonatal period and school age. The results of this work showed that the red-bone-marrow-containing cancellous bone layer reaches its greatest thickness in the manubrium of the sternum. Sternal puncture in children should be performed in the upper third of the manubrium sterni, in the midline.

Cholecystography in children O primenenii kholetsistografii u detei. KOSTIN O. S. *Pediat. Akush. i Ginek.* 1956, 6 (9-12).

Fifty-four children, 3 to 16 years of age, were examined; forty-five of them suffered from cholangiocystitis; two, from gastritis, and seven were healthy controls. The author employed the Soviet preparation Bilitrast, in doses of 0.06 to 0.065 gm. per kilogram of body weight. The advantage of this preparation is its peroral administration, resulting in less trauma to the children and producing no complications. In the control group of children the cholecystography revealed a gallbladder of pyriform shape, situated at the level of the second to fourth lumbar vertebrae; in vertical position of the patient the gallbladder emptied within 1 to 1½ hours. In children with cholangiocystitis a variety of gallbladder shapes were observed: cylindrical, conical, etc. Cholecystograms showed an enlargement and deformation of the gallbladder, as well as retardation of its emptying; in children with cholangiocystitis the emptying occurs between 30 minutes and 2½ hours, sometimes even later. Also, disturbances of the motor function of the gallbladder were noted, which is a valuable diagnostic sign in diseases of the biliary tract.

Methodology of cholecystography in children Metodika kholetsistografii u detei. KURBATOVA M. D. *Pediatriia* 1956, 6 (24-27).

Preliminary results are given of cholecystography employing Bilitrast (iodophthalein Na) in children of various age groups (3 to 15 years). The method of investigation and of preparation of the patient is described in detail. Bilitrast is given in capsules, the dose being calculated as 0.05 gm. per kilogram of body weight, the total not exceeding 2.0 gm. The average dose for a child was 1.5 to 1.8 gm. in three doses at intervals of 20 minutes. No side-effects were observed. With a suitable and careful preparation of patients and of Bilitrast dosage, this method will completely replace intravenous cholecystography, which produces a series of unpleasant side-effects.

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News and Comment

GENERAL NEWS

Specialists Certified by the American Board of Pediatrics, Inc.—The following physicians were certified as specialists by the American Board of Pediatrics, Inc., in Cincinnati, June 13, 14, 15, 1958.

Adams, Julius T., San Francisco.
Adler, Philip, Detroit.
Anderson, Lewis Bruce, Jr., Billings, Mont.
Andrus, Bailey C., Kansas City, Mo.
Bauer, Charles H., New York.
Belt, James Harvey, Indianapolis.
Bolinske, Robert Edward, Columbus, Ohio
Buzan, Edwin F., Alton, Ill.
Carter, Harvey Lee, San Diego, Calif.
Ching, Alfred Y. T., Ann Arbor, Mich.
Cilella, C. A., Chicago.
Cline, Alan L., Pontiac, Mich.
Cohn, Bradford Philip, San Francisco.
Collins, William R., Jr., New Bedford, Mass.
Crea, Maria Antoinette, Cleveland.
Daly, Joseph Michael, Indianapolis.
De Garmo, Albert H., Cincinnati.
Dorgelo, Gerhard H., Trail, B. C., Canada
Eisenberg, Nathan P., Columbus, Ohio
Englert, James Joseph, Cincinnati.
Falliers, Constantine John, Denver.
Fox, Mary Alice Vann, Bethesda, Md.
Freeman, Raymond S., Denver.
Gall, John Christian, Jr., Miles City, Mont.
Gauchat, Robert David, Iowa City.
Gerlach, Julius Andrew, Jr., Cleveland.
Glaser, James Vincent, Granada Hills, Calif.
Good, Robert Francis, Dravosburg, Pa.
Greenberg, Robert Eric, Syracuse, N. Y.
Grossman, Herman, Oradell, N. J.
Hamady, Alfred, Battle Creek, Mich.
Hanson, Thomas A., Tacoma, Wash.
Harvey, Birt, Palo Alto, Calif.
Haynes, Ralph E., Bluefield, W. Va.
Higgins, Clarence Ronald, Jr., Merced, Calif.
Howard, Cecil Byron, Maryville, Tenn.
Kaplan, Martin J., Highland Park, Ill.
Kaster, John David, Hillsborough, Calif.
Kultzen, Ingeburg G. A., Lodi, Calif.
Langley, Leslie W., Jr., Somerset, Ky.
Mackoff, Leslie, Seattle.
McKeon, Edward C., Washington, D. C.
Medearis, Donald Norman, Jr., Baltimore, Md.
Mellins, Robert Bère, Tarrytown, N. Y.
Miller, Joseph Boxley, Jr., Yazoo City, Miss.
Nitchals, Jeanne Elizabeth, Cincinnati.
Norton, Clayton, Arnold, Md.
Pipkin, Fred, Louisville.
Polley, Robert F. L., Seattle.
Rosa, Franz Weston, APO 205, N. Y.
Rosenthal, Joseph Hyman, Orinda, Calif.
Rovnanek, Agnes Jean, Salt Lake City.
Schwab, Louis, Cincinnati.
Shiller, Jack G., Westport, Conn.
Simon, David Leo, St. Louis.
Steinman, Arnold Miller, Pittsburgh.
Sturtz, George Stephen, Watertown, N. Y.
Szeto, Isabel Lai-Fong, Pittsburgh.
Tall, Milton G., Baltimore.
Thomas, Allan Perry, Salt Lake City.
Thompson, Spencer Gwaine, Urbana, Ill.
Turner, James K., Clayton, Mo.
Turner, Richard Eugene, Springfield, Ore.
Upp, James R., Biloxi, Miss.
Vrla, Vlastimil, Park Forest, Ill.
Walsh, S. Zoe, New York.
Weitemier, Raymond Arthur, Richmond, Ind.
Whitcomb, John H., Pensacola, Fla.
Wilson, John Francis, Cincinnati.
Wilson, Lewis Grant, Los Angeles.
Young, John Thomas, Travis AFB, Calif.

The following candidate passed the examination in Memphis in March, 1958, but was not eligible to receive certificate until July 1, 1958.

Kamin, Sheldon, Chicago.

Special Foreign Certificates were given to the following physicians.

Canlas-Dizon, Fe, Manila, Philippines
Carretero, Rosario, Manila, Philippines
Choy, Peter Wai Shuen, Hong Kong
Garcia, Liborio, San Juan, Rizal, Philippines
Haddad, Heskel M., Givataiim, Israel
Kumar, Bharat Bhushan, Omaha.
Makkia, Mahdy, Baghdad, Iraq
Mazumdar, Harish, Brooklyn.
Morales, Adoracion Concepcion, Manila, Philippines.
Vallbona, Carlos, Barcelona, Spain
Vera Cruz, Pio G., Quezon, Philippines
Wadhwani, Kishin Vishindas, Harding, Mass.
Manonmani, Kariagounder, Brooklyn.
Reyes, Priscila C., Chicago.

New Institute to Study Communication Among Medical Scientists.—The Institute for Advancement of Medical Communication, a nonprofit organization, was recently formed to study and develop ways to increase the efficiency of information exchange among medical scientists, medical educators, and practicing physicians. The greatly accelerated pace of medical research today requires new techniques and media to handle the ever-increasing flow of knowledge. The Institute proposes to speed development of the necessary communication methodology by devising and testing methods of disseminating medical information which promise advantages over those in present use and by serving as an information center for medical organizations which desire help with communication problems. The work of the Institute will be financed by general and research grants from private foundations and from agencies, private and federal, which support medical research.

The charter members of the Board of Directors are Chauncey D. Leake, Ph.D., Professor of Pharmacology and Assistant Dean, College of Medicine, Ohio State University; Homer W. Smith, Sc.D., Professor of Physiology, New York University, College of Medicine, and Irving S. Wright, M.D., Professor of Clinical Medicine, Cornell University. Richard H. Orr, M.D., Assistant Editor of the journal *Metabolism* and formerly Medical Director of Grune & Stratton, Inc., will serve as Executive Director. An Advisory Board, consisting of a panel of experts in the various techniques and disciplines concerned with medical communication, is in the process of being selected.

The temporary headquarters of the Institute are at 37 E. 67th St., New York 21. Further details, if desired, may be obtained by contacting the Executive Director.

Labeling Hazardous Substances in Packaged Chemicals.—The growing demand for uniform legislation to require precautionary labeling of all chemical products which are not now so regulated was discussed at the first legislative conference, held on May 9, 1958, at the American Medical Association headquarters. Speaking to government, industry, and medical representatives from approximately 40 national organizations, members of the A. M. A. Committee on Toxicology discussed the "Uniform Hazardous Substances Act" and compared it with other tentative legislation which has been proposed.

Attention was focused on the general nature of the problem, as seen by the medical profession, public health officials, and the public and by remarks from a pediatrics representative and officials of the American Public Health Association and the National Safety Council. The principles which the Committee employed in formulating the provisions of a model law for labeling all types of hazardous substances were next reviewed. A comparison of the model bill with other tentative legislative proposals followed.

An industry-wide label law conference was held on July 25, 1958, under the sponsorship of the Committee on Toxicology. The second meeting discussed proposed legislation requiring the declaration of hazardous ingredients and warning statements on the label and in the accompanying literature of household, commercial, and industrial packaged chemicals. Over 100 organizations, including representatives of trade associations, toxicity testing laboratories, chemical trade unions, and other interested groups, were invited to participate.

This was the second of several meetings which will be held to discuss proposals for local and federal regulations to close the gap in label legislation. A Committee survey showed a sketchy, nonuniform, and generally inadequate pattern of labeling regulations at the state and national level. Ninety per cent of the states lacked requirements for precautionary labeling of commercial as well as household chemical products. These meetings were held to bring about a clearer understanding of what the model bill is intended to cover and the benefits to be derived from such legislation.

ANNOUNCEMENTS

Residency in Pediatric Oncology.—Applications for the residency from July 1, 1959, to Dec. 31, 1959, in pediatric oncology at Memorial Center for Cancer and Allied Diseases in New York will be received up to Nov. 1, 1958. This residency is approved for partial credit by the American Board of Pediatrics and is limited to the neoplastic diseases of children. Salary: $3600 annually plus maintenance. For application forms and information write to Director, Pediatric Service, Memorial Center for Cancer and Allied Diseases, 444 E. 68th St., New York 21.

Books

BOOK REVIEWS

Year Book of Cancer (1956-1957 Year Book Series). Compiled and edited by Randolph Lee Clark Jr. and Russell W. Cumley. Price, $7.50. Pp. 572, with 210 illustrations. The Year Book Publishers, Inc., 200 E. Illinois St., Chicago 11, 1957.

The "Year Book of Cancer" consists of a series of selected abstracts of recent articles about the various types of malignancies. These abstracts are followed by appropriate critical comments by the authors. These abstracts are complete summaries of the articles and cover most of the types of tumors and the organ systems. The articles cover mostly the clinical and therapeutic side, but more basic material is also covered.

DEMETRIUS G. TRAGGIS, M.D.

The Infantile Cerebral Palsies. By Eirene Collis, W. R. F. Collis, William Dunham, L. T. Hilliard, and David Lawson. Price, $3.00. Pp. 100. Charles C Thomas, Publisher, 301-327 E. Lawrence Ave., Springfield, Ill., 1957.

This small, compact book of one hundred pages has been written by the "Little Committee for the study of the Infantile Cerebral Palsies," consisting of Eirene Collis, W. R. F. Collis, W. Dunham, L. T. Hilliard, D. Lawson, and Sir Francis Walshe. The last has written the foreword, stating that the "basic problem in the treatment of cerebral palsy is clearly expounded by the authors. It is a problem in applied neurophysiology."

The authors discuss the importance of Little's original observations and deductions, devoting a chapter to show that his work is not only of historical but of practical value at the present time.

It is obvious that the authors have had much experience with cerebral palsy cases. They describe five varieties: (*a*) generalized spasticity, (*b*) hemiplegia, (*c*) variable rigidity, (*d*) athetoid cerebral palsy, and (*e*) ataxic cerebral palsy (very rare). Each variety is described in detail, and examples of typical cases are given. In addition, a scheme of management is outlined, particularly instructions to parents. These instructions should be very helpful to therapists directing treatment or actually treating children with cerebral palsy.

From various studies in Europe, the incidence of cerebral palsy is placed at 2 per 1000 live births. An outline of the organization of cerebral palsy services in England is given, and it is assumed from the work of Ingram that 25% of cases are of normal intelligence, 25% are grossly mentally defective, and the remaining 50% will require special education.

The book is short, easily read, and full of information. It should be useful to students, practitioners, pediatricians, and physical therapists.

HADDOW KEITH, M.D.

Year Book of Pediatrics (1957-1958 Series). Edited by Sydney S. Gellis, M.D. Price, $7.50. Pp. 469. The Year Book Publishers, Inc., 200 E. Illinois St., Chicago 11, 1957.

Once again, Dr. Gellis has done an excellent job in selecting and abstracting significant papers in pediatrics from the previous year's publications. The book is effectively organized, having chapters devoted to papers on the premature and newborn, nutrition and metabolism, infectious disease and immunity, and so on. An added virtue is the inclusion of relevant papers from fields such as ophthalmology, orthopedics, neurology, psychiatry, therapeutics, and toxicology.

Commendable is the inclusion of some papers of research nature. They add a special value for the pediatrician who often has too little time available even for perusal of his clinical journals.

The commentaries or discussions by recognized authorities following many of the abstracts are invaluable. Effective checks and balances for the evolution of scientific truth, these commentaries not only provide support for the authors' opinions but also may explain a contradictory stand.

The paper is of good quality; hence photographs and roentgenograms lose little or nothing in reproduction.

In my opinion, this book, as edited by Gellis, continues to be a little gem of great practical value to all in pediatrics, whether interns, residents, or practitioners. I recommend it enthusiastically as a supplement to pediatric texts and periodicals.

EDMUND C. BURKE, M.D.

Clinical Enzymology. By Gustav J. Martin, Sc.D. Price, $6.00. Pp. 241, with 5 illustrations. Little, Brown & Company, 34 Beacon St., Boston 6, 1958.

For many of us practicing physicians the term "enzymes" refers to vague chemical substances found in the laboratories of the biochemists. Many use the term as an even more vague explanation for certain phenomena. How often does one hear the following: "No one knows what the explanation is. It must be an enzyme"!

It is an arresting experience, therefore, to come across a book with the title "Clinical Enzymology," and it is impressive to read how much of clinical science from both the diagnostic and therapeutic aspects is directly involved with enzymology today. Consider, for example, the parenteral use of trypsin in occlusive peripheral vascular disease. The book presents impressive "before and after" pictures illustrating its use parenterally in cases of decubitus ulcers, thrombophlebitis, and varicose ulcers. However, as in many other fields, the interpretation of the results of studies in which this agent was used are not always clear cut. Nor do the opinions presented always present a unanimous consensus. However, both sides of the picture are presented, and no attempt is made to mislead the reader. Its use in ophthalmologic diseases, "rheumatic" disease, and gastrointestinal disorders is also outlined, and a discussion is given of its toxic effects. Similar discussions are also given of the clinical uses of chymotrypsin, streptokinase, deoxyribonuclease, hyaluronidase, and cholinesterase.

Another chapter (in which the pediatrician will perhaps find himself on more familiar ground) deals with the diagnostic use of enzymes. A detailed description is given of the diagnostic use of measurement of amylase, trypsin, and antithrombin in pancreatic disorders, lysozyme in peptic ulcer and ulcerative colitis, hyaluronidase and antihyaluronidase in rheumatic fever, uropepsin in peptic ulcer and pernicious anemia, cholinesterase in liver disease and malnutrition, transaminase in myocardial infarct, acid phosphatase in prostatic disorders, and alkaline phosphatase in liver and bone disorders.

To be sure, much more is known about enzymes than their clinical applications, and the book contains absorbing chapters (for those with sufficient persistence and determination to pursue the subject) on the chemistry of enzymes and (as a separate entity) their biochemistry. This segment is somewhat less conventional than that found in standard texts on enzymes, and some rather philosphical views relating not only to enzymes but to the physical sciences in general are included. After noting in passing for example, that when quantum physics displaced classical physics the physicist was at once "chained and freed," one of the five contributing authors refers to the biological equivalent of the Pauli exclusion principle of electronic configuration and a current concept that enzymes and their substrates do not necessarily fit exactly like a lock and key as Emil Fischer once said. Rather ". . . the forces exerted by the spatial and directional requirements of valence bonds enable the lock or key to change dimensions so as to accommodate each other." This is given as a biological example of the exclusion principle. Much more is said about current concepts of enzyme action. The clinician who would like to get more factual information on enzymes is referred elsewhere. For interesting and dynamic writing in this none too easy field, however, this book probably has few equals.

S. A. KAPLAN, M.D.

Tracheotomy: A Clinical and Experimental Study. By Major Thomas G. Nelson (MC), U. S. A. R. Price, not given. Pp. 111. The Williams & Wilkins Company, Mount Royal & Guilford Aves., Baltimore 2, 1958.

The author presents a careful history of the evolution of the surgical procedure, with a detailed discussion of the everexpanding number of conditions in which tracheotomy properly is utilized to correct both mechanical respiratory obstruction and secretional ventilatory obstruction. It is noted that each year the use of tracheotomy in the treatment of secretional ventilatory obstruction increases, while its use for mechanical respiratory obstruction remains at a fairly constant incidence.

A series of 310 tracheotomies performed on a group of 300 patients is rather thoroughly evaluated with regard to indications for, performance of, and complications resulting from the various methods used to create tracheostomies. Techniques are described, discussed, and

evaluated from both the clinical and the experimental standpoints. The conclusions derived from the study are presented in a concise and lucid fashion, and so one is able to benefit from vast experiences gained by others. Certainly this volume is a very worth-while contribution to the literature on tracheotomy, and, in addition, the bibliography is exceptional.

JOHN C. LILLIE, M.D.

Roentgen Diagnosis of Abdominal Tumors in Childhood. By Charles M. Nice Jr., M.D., Ph.D.; Alexander R. Margulis, M.D., and Leo G. Rigler, M.D. Price, $4.00. Pp. 75, with 95 illustrations. Charles C Thomas, Publisher, 301-327 E. Lawrence Ave., Springfield, Ill., 1957.

This volume thoroughly covers the roentgenologic aspects of abdominal tumors in childhood. The book emphasizes the importance of the so-called plain roentgenogram of the abdomen with the variations in position of the patient that are often helpful in diagnosis. I believe that this emphasis is correctly placed.

There is a brief description of anatomy and embryology, with particular reference to the development of secondary attachments of the mesentery and peritoneal reflections, illustrated by diagrams.

The various roentgenologic procedures available to aid in diagnosis are then reviewed, with some estimation of the value of each in the demonstration of certain lesions.

The classification and incidence of abdominal masses is brief but sufficient, since the book deals primarily with roentgenologic diagnosis.

Intra-abdominal masses are divided into (1) those in the region of the liver, (2) other intraperitoneal masses, (3) renal and adrenal masses, and (4) other extraperitoneal masses. Each section is illustrated well, and the roentgenographic reproductions are such that the lesions can easily be seen.

A good bibliography and subject index is included, and the print is easy to read.

Though the reading time is short, the book is concise and contains much information worthy of a second look.

The book is recommended particularly to radiologists, pediatric surgeons, pediatricians, and students not only for casual reading but for study.

JOHN R. HODGSON, M.D.

Rehabilitation of the Cardiovascular Patient. By Paul Dudley White, M.D.; Howard A. Rusk, M.D.; Philip R. Lee, M.D., and Bryan Williams, M.D. Price, $7. Pp. 176. McGraw-Hill Book Company, Inc., 330 W. 42d St., New York 36, 1958.

This very readable little book is addressed primarily to physicians, to encourage and help them in rehabilitation of cardiovascular patients. It emphasizes that the physician must take the responsibility for rehabilitation of his patient. This may mean a simple referral to a competent clinic or an involved, long-range program carried out mainly by a lone physician, as is still necessary in many, if not most, parts of the United States. Many concrete suggestions are given to help the physician on his own, especially in dealing with the patient with hemiplegia or hemiparesis.

The child with heart disease is discussed briefly in two short chapters on rheumatic and congenital heart disease. There still appears to be no objective way of deciding what restrictions, if any, need be placed on the child with heart disease. The statement is made, however, that adults with rheumatic heart disease may work successfully in jobs requiring strenuous physical labor for a period of years before becoming vocationally handicapped. Thus it is suggested that "children should be counseled early to accept the maximum academic or vocational education of which they are capable so that a reasonable range of vocational opportunities will be open to them and additional training will not be necessary in middle life."

ELAINE ALLEN, M.D.

Cerebral Palsy in Childhood. By Grace E. Woods, M.D. Price, $6.50. Pp. 158. John Wright & Sons, Ltd. (The Williams & Wilkins Company, Mount Royal and Guilford Aves., Baltimore 2, U. S. agents), 1958.

In writing this book, the author attempts to analyse the various etiological factors contributing to occurrence of cerebral palsy in childhood. In order to make a total clinical assessment of the child with cerebral palsy, she also evaluates the associated clinical defects, such as sensory loss or hearing deficit, in addition to the neuromuscular involvement. The data in the book are based on a group of 301 children seen at the Cerebral Palsy Assessment Clinic of the

Bristol Children's Hospital, Bristol, England. These children were examined by a team of workers whose purpose was to evaluate each child for educability and proper placement. The average number of children with cerebral palsy who reached the age of 5 years in the period 1930-1951 was 1.90 per 1000 live births in Bristol.

Cases of cerebral palsy are discussed under the headings of (*a*) paraplegia, (*b*) monoplegia, (*c*) hemiplegia, (*d*) quadriplegia, (*e*) athetosis, (*f*) ataxia, and (*g*) rigidity. In the paraplegia group, all spastics, there were 26 patients. Three cases were genetically determined; in thirteen prematurity appeared significant. Other factors were birth trauma in four cases and postnatal infection in two cases. The monoplegias included 13 cases, either spastic or flaccid, all involving one leg. The etiology appeared to be similar to paraplegia. The spastic hemiplegia group included 97 patients. Of these, 66 had a high incidence of abnormal birth, neonatal asphyxia, and neonatal illness. Twenty-eight cases followed postnatal illness in infancy. There were 75 cases of spastic quadriplegia. A few were genetically determined. The etiological factors were varied, including prematurity, antenatal illness, antepartum hemorrhage, a significant increase in the incidence of a first birth to an older mother, neonatal asphyxia or jaundice, and both very low and excessively high birth weights. Thirty-three cases of athetosis were included, due primarily to abnormalities at the time of delivery. The ataxic group included 29 heterogeneous cases. In the 28 rigidity cases there was a high incidence of associated congenital defects and antenatal illness.

In the remaining chapters of the book visual, auditory, and sensory defects are discussed. There is a chapter on epileptiform disturbances and a final one on the assessment of educability. There is a good chapter on the history and related literature of cerebral palsy and a fairly complete bibliography.

The impressions of the author are in general agreement with previously published articles on the etiology of cerebral palsy. Since her conclusions are based on a retrospective study of each case history, there are the usual limitations, including lack of early notations as to the conditions at delivery or the state of the baby at birth. The author is aware of these problems and offers this study as a clinical estimate based on a small number of cases.

The book may well be recommended as an introduction to the general understanding of cerebral palsy. It emphasizes the need for considering the associated problems of lowered I. Q., impaired hearing and vision, behavior abnormality, seizures, and learning and perceptual difficulties, which are so significant in addition to the neuromuscular impairment.

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1. Breslow, L.: Clinical Approach to Infantile Colic. J. Pediat. 50: 196-206, 1957. (Reprint sent on request.)

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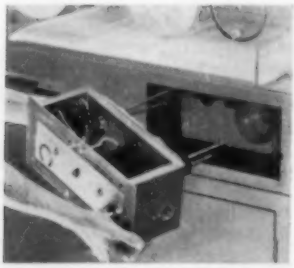

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- Removable power unit
- Molded plastic entry ports

The new model C-77 Isolette infant incubator has been designed to provide many important new features while retaining all the precise atmospheric controls of the earlier model. In addition all ISOLETTE accessories—the VAPOJETTE®, ISOLETTE ROCKER, and weighing scale—fit the new C-77 ISOLETTE.

of the NEW *Isolette*®

infant incubator by *AIR-SHIELDS, INC.*

To provide every advantage for the new-born or premature infant . . .

THE NEWLY DESIGNED ISOLETTE infant incubator (Model C-77) retains and refines *all* the outstanding advantages of the earlier model, and provides many important new features as well:

True isolation—(1) by use of air from *outside* the hospital or, (2) by use of the new MICRO-FILTER which removes 99.50% of contaminants as small as 0.5 micron (average *staphylococcus* is 0.8 micron*) from *nursery* air. Thus, a constant supply of pathogen-free air from outside the hospital, or micro-filtered nursery air safeguards the infant from air-borne or droplet infection.

Easily cleaned—one-piece, smooth aluminum conditioning chamber, with rounded inside corners—no inaccessible areas to become contaminated with bacteria.

Relative humidity control—simple to operate and easy to clean—maintains stable R.H. as high as 85% to 100%, independent of temperature.

Temperature control within ±1°F.

Efficient cooling system ensures safe incubator temperatures even when nursery temperature exceeds 95°F.

Unique O_2-limiting valve—restricts concentration to 40% even when high flows are used by unique "relief" valve which bleeds excess oxygen outside the ISOLETTE. Low or high concentrations can also be maintained.

Removable power unit—compact, lightweight power unit containing heating element, operating and safety thermostats, and air-circulating blower fits snugly into conditioning chamber. The new power unit is easily removed for replacement of parts.

For additional information about the *new, model C-77* ISOLETTE, phone us collect (OSborne 5-5200) or write AIR-SHIELDS, INC., Hatboro, Pa.

*Zinsser, H.: Bacteriology, ed. 11, New York, D. Appleton-Century Co., Inc. 1957, p. 244.

FOR CONSTIPATED BABIES

Borcherdt

MALT SOUP EXTRACT

Provides quick, safe, gentle relief with no gas pains, no stomach upset and no side effects. This time-tested product, by developing friendly aciduric intestinal flora, gets very satisfactory results NATURALLY.

Two tablespoonfuls in the daily formula for infants (in water for breast fed babies) produce soft, natural stools. Malt Soup Extract is very effective also for growing children when added to cereals, fruit juices or milk.

Malt Soup Extract is specially processed non-diastatic barley malt extract neutralized with potassium carbonate. It has been time-tested for more than forty-five years.

Available in both powder and liquid forms in 8 ounce and 16 ounce jars.

WE WILL BE GLAD TO SEND SAMPLES

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217 North Wolcott Avenue, Chicago 12, Illinois

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the unique nitrofurans eliminate

problem pathogens

problem pathogen: Staphylococcus aureus

"The ability of this organism to adjust to its antibiotic environment is one of the major problems in medicine today."*

FURACIN CASE REPORT: STAPHYLOCOCCAL OSTEOMYELITIS

Severe compound fracture of right foot led to a large, open ulcerated wound on the sole, with tarsal bones exposed and necrotic. Despite extensive debridement, removal of necrotic bone and attempted closure with a pedicle flap, the wound failed to heal and developed considerable purulent drainage.

Culture of pus revealed Staphylococcus aureus, *resistant to all antibiotics tested*, but sensitive to FURACIN. Daily irrigation was instituted, employing 1 part of FURACIN Solution to 4 parts normal saline. Depths of the wound were reached with a long #20 needle on a 20 cc. syringe.

Purulent drainage decreased considerably within a few days, stopped completely after 2 weeks of irrigation with FURACIN Solution. The open space beneath the pedicle flap gradually filled with healthy granulation tissue, and 6 weeks after institution of FURACIN treatment, healing was complete.

In clinical use for more than 12 years and today one of the most widely prescribed topical antibacterials, FURACIN—like other nitrofurans—remains effective against pathogens which have developed, or are prone to develop, resistance to antibiotics.

The NITROFURANS

Products of
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FURACIN® brand of nitrofurazone

Available as Soluble Dressing, Soluble Powder, or Solution. Also in Vaginal and Urethral Suppositories and in special formulations for eye, ear and nose.

*Koch, R., and Donnell, G.: California Med. 87:313, 1957.

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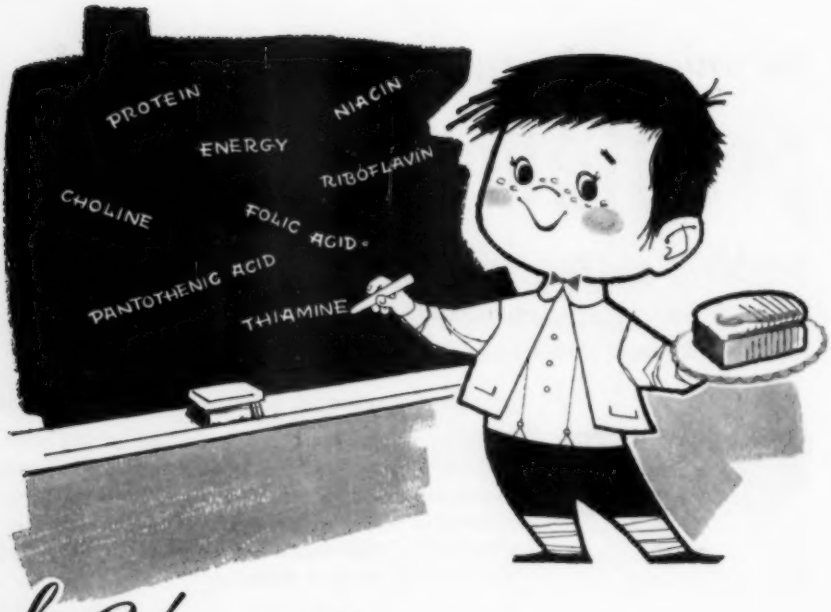

So Versatile

Children love the softness, the sunny taste of Enriched Bread. They appreciate it as a vehicle for so many other foods.

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Enriched Bread

is a basic food in virtually every diet in health and disease...in childhood and throughout life.

*Thiamine, riboflavin, niacin, pantothenic acid, choline, folic acid, and other B-complex factors.

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*WORMS HATE 'EM

No fasting • No special diets • No purging

The new Piperazate Wafers, utilizing insoluble piperazine *phosphate*, provide short, pleasant piperazine treatment for intestinal helminths. For pinworm, *only one dose a day* for just *one week* is required; for roundworm, *a single dose*.

Kids love the cool, tasty mint flavor of Piperazate Wafers. There is no possibility of spillage or variation in the size of the dose. And the use of Piperazate avoids the high incidence – 35-50% – of nausea, vomiting and diarrhea which may be associated with gentian violet therapy.[1]

Piperazate assures a 90% cure rate in one week's treatment of pinworm[2] and an 85% cure rate in one day's treatment of roundworm.[3]

One Week Dosage for Pinworm	One Day Dosage for Roundworm
Children 15-30 lbs. . . . 1 Wafer	Children 20-30 lbs. . . . 3 Wafers
Children 31-60 lbs. . . . 2 Wafers	Children 31-40 lbs. . . . 4 Wafers
Children 61 lbs. and over . . . . . 4 Wafers	Children over 40 lbs. and adults . . . . . 7 Wafers
To be sucked or chewed before breakfast for 7 consecutive days.	To be taken at one time on one day only.

Piperazate* Wafers

piperazine phosphate, Leeming, 500 mg.

Supplied: In packages of 28 Wafers

1. Goodman, L., and Gilman, A.: Pharmacological Basis of Therapeutics, New York, Macmillan, 1955, p. 1153. 2. Brown, H. W., *et al.*: J.A.M.A. *161*:515 (June) 1956. 3. Hoekenga, M. T.: World M. J. *3*:299 (Sept.) 1956.

*TRADEMARK

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Open spaces are no help in breathing, when nasal passages are shut tight from pollen or with head colds.
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HYDROCHLORIDE
Pediatric Nasal Spray
0.25% · 20 cc.
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In the handy plastic squeeze bottle
Prompt and Prolonged Decongestion
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